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CONSULTATIONS IN

FELINE INTERNAL MEDICINE

Volume

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John R. August

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This book is dedicated to the memory of my father, George August.

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PREFACE

During orientation at the beginning of each 2-week student rotation on our feline internal medicine service, I prime the group with three nuggets of wisdom about feline practice. First, sick cats surrender clues about their illnesses very reluctantly; hence, the tenet that the foundation of good feline medicine is a meticulous history and physical examination. Second, you have to be a good ear, nose, and throat doctor to thrive in feline practice, given the nagging propensity of cats to develop chronic upper airway problems. Third, our clients expect us to respect the central roles that their cats play in their families. Subsequently, we must communicate with our clients not only as veterinarians but also as pediatricians.

Each volume of *Consultations in Feline Internal Medicine* complements previous books in the series. During initial planning, I asked the ten section editors to identify topics in their respective specialty disciplines that would be of unique importance to progressive feline practitioners in 2006 and beyond. The selection of topics in this book is broad, eclectic, and in some cases purposely controversial. Although the focus of the series always has been to provide cutting-edge information about medical disorders, the books also provide a platform for reflective discussion about contentious public issues, for example, cruelty, and the effect of cats on wildlife populations.

I learn so much about cats and their diseases by reviewing the manuscripts that are submitted for the book. It is a genuine privilege to work with an esteemed group of section editors and authors, all of whom are leaders in the discipline of feline studies, and they deserve my heartfelt thanks for the quality of their contributions to the project and for their respect for the tight deadlines that we imposed. The attractive and contemporary design of the fifth volume, and the liberal inclusion of high-quality color illustrations, reflect the exemplary standards of the publishing team at Elsevier. My very special thanks go to Dr. Anthony Winkel, Editor, Veterinary Medicine; Ms. Shelly Stringer, Developmental Editor; and Mr. David Stein, Project Manager. Keeping up with the flow of hundreds of digital files from around the world has been a daunting challenge, but one made much easier through the guidance, patience, and expertise of these colleagues. Lastly, I must thank my wife, Janet, who graciously tolerated the weekends and evenings that I spent editing manuscripts in my home office, when I really should have been helping her with a burgeoning list of tasks around our home.

As I look around the cages of our feline internal medicine ward, I continue to be amazed at the true beauty of the cats under our care. The dazzling array of exotic hair coat patterns would be at home in any jungle setting, reminding me that many of my patients have been domesticated grudgingly. It is no wonder then that the evolving healthcare of this mysterious species provides us with so many professional challenges and rewards.

John August
College Station, Texas

John August

Chapter 1

CALICIVIRUS: SPECTRUM OF DISEASE

Janet E. Foley

Caliciviruses are among the most common problematic infectious agents of cats, with extraordinarily high rates of infectivity, morbidity, and death. Although vaccination against caliciviruses is practiced commonly, these vaccines have incomplete efficacy and can contribute to minor morbidity. Caliciviruses are responsible for diseases ranging from acute nuisances and cattery problems to chronic debilitating problems to peracute fatal emerging problems. The following pages review salient aspects of the biology of feline caliciviruses (FCVs), present some characteristics of calicivirus-associated clinical syndromes in cats, and discuss problems with detection and management of these infections.

BIOLOGY OF FELINE CALICIVIRUS

FCV is an RNA virus, characterized by high rates of mutation and high antigenic and genetic diversity. Caliciviruses are nonenveloped, positive-sense, single-stranded RNA viruses and include FCV, rabbit hemorrhagic disease virus (RHDV), and vesicular exanthema of swine virus. The name calicivirus derives from the appearance on electron microscopy of a series of cup (calyx)–like depression in the virus surface. The virus is rather simple genetically, with two large and one small open reading frames. Like other members of the family Caliciviridae, FCV is prone to high mutation rates and minimal repair, a mechanism that has been implicated in the previous emergence of RHDV.[1] Antigenic change and the emergence of FCV quasispecies have been reported previously during persistent infection with FCV.[2,3] One of the large open reading frames encodes a unique single structural capsid protein which functions in RNA and host cell attachment. The virus has numerous arch-like capsomeres, each of which is a capsid protein dimer.[4] FCV antigenic types are diverse, although strain F9 is rather broadly antigenically cross-reactive.[5] Cats that have been infected with one strain may not be protected against antigenically dissimilar strains. The ability of FCV to induce disease is due directly to the virus and also to immune-mediated complications.

RESPIRATORY TRACT INFECTION

The most commonly recognized clinical problem attributable to FCV is upper respiratory tract infection (URI) (Figure 1-1). In one shelter, 55 per cent of all cats had URI, including 24 per cent with severe URI[6] (Figure 1-2). Etiological testing for agents of URI is performed uncommonly, but previous studies have implicated at least five pathogens as causative agents of feline URI: FCV, feline herpesvirus type 1 (FHV), *Mycoplasma* spp., *Chlamydophila felis,* and *Bordetella bronchiseptica.*[7-12] In shelters and catteries, FCV may be isolated frequently, with rates as high as 50 per cent in some shelters and an average shelter isolation rate of 28 per cent,[6] although many infected cats appear healthy. This is consistent with isolation rates reported elsewhere.[7,13-15]

FCV infection usually is transmitted by aerosol; the virus is introduced into a cat via oral and nasal routes. Subsequently, the virus spreads systemically with viremia and high levels of virus secretion from many sites, including saliva, respiratory secretions, feces, and urine. At a minimum, shedding occurs for approximately 2 weeks and, commonly in shelters or in kittens, for months. Concurrently, cats develop lymphopenia and neutropenia.[16] Infected cats may show no immediate clinical signs or develop high morbidity, and they may recover uneventfully within weeks, develop chronic infections with chronic morbidity, or appear well and eventually develop reactivated signs.

Acutely affected cats often develop fever, conjunctivitis, rhinitis (although both conjunctivitis and rhinitis are more typical of FHV infection than FCV), and vesicular stomatitis, including glossitis, faucitis, and palatitis (Figures 1-3 and 1-4). Vesicles rupture within hours to days; therefore, observation of small inflamed, painful erosions is more typical. Neutrophils infiltrate the edges of the necrotic ulcers, which usually heal within several days to weeks. Coinfections tend to exacerbate disease severity: concurrent FHV and FCV reportedly induced more severe signs of URI,[6,17] and FIV also has been described as a potentiator of more severe signs.[16]

About 25 per cent of FCV-infected cats develop chronic infection,[18] whereas as many as 50 per cent appear to shed virus

Figure 1-1. Kitten with severe URI, with hunched posture typical of difficulty breathing, sunken ocular globes, dehydration, fever, and depression. (Courtesy Kate Hurley and Mike Bannasch, UC Davis Shelter Medicine Program.)

Figure 1-2. Cat with severe URI, with photophobia and conjunctivitis as well as purulent ocular-nasal discharge. (Courtesy Kate Hurley and Mike Bannasch, UC Davis Shelter Medicine Program.)

chronically after infection.[19] Some of the variance in clinical severity could be due to genetic differences in the infecting viruses, in addition to the individual cat's immune system's response to infection. In all endemically infected populations, the FCV isolates exhibit a large amount of genetic variation, often with some isolates that cluster genetically with the vaccine strain.[6,20] Possible mechanisms for apparently chronic infection could be poor or inadequate immunity (often deriving only from relative immaturity), reinfection with antigenically dissimilar strains of FCV, or emergence of genetic variants or quasispecies, evading host immunity[3] (although the latter phenomenon could be a symptom rather than a cause of chronic infection).

A complication of mild upper respiratory tract infection is lower respiratory disease associated either with FCV alone or more often FCV and secondary bacteria such as *B. bronchiseptica, Escherichia coli,* or others. In one study of feline

Figure 1-3. Cat with severe purulent nasal discharge associated with URI. (Courtesy Kate Hurley and Mike Bannasch, UC Davis Shelter Medicine Program.)

bordetellosis, most cats with lower respiratory tract bacterial infection were coinfected with FCV.[21] Lower respiratory FCV disease more typically is an individual animal problem rather than a herd disease and occurs most often in young kittens. The lungs may become congested and edematous and eventually consolidate. The initial lesion is focal alveolitis, which generalizes to exudative, then proliferative, interstitial pneumonia.[22] If the lungs do not develop secondary bacterial infection, the condition may resolve without intervention other than supportive care.

STOMATITIS AND POLYARTHRITIS, IMMUNE COMPLEX DISEASES

Cats with FCV may suffer from polyarthritis or stomatitis, both commonly believed to be immune-mediated complications of infection (Figure 1-5). Often on about the second day of FCV infection with URI, the cat exhibits a transient fever and shifting-leg limping associated with pain on ambulation. Affected cats usually have oral lesions and are better within 3 to 4 days; histologic lesions are absent from the joints,[23] although the joints have thickened synovium and increased synovial fluid. The pathogenesis of this lesion is not known. A second polyarthritis scenario occurs starting about 10 days to 3 weeks after infection in which immune complex polyarthritis may occur. This syndrome often occurs in the absence of contemporaneous URI lesions and may be identified initially in a cat that presents merely with anorexia, lethargy, and possibly fever. Anecdotal reports suggest this syndrome also may occur in cats that have been vaccinated recently (within 1 month) for FCV. The problem may be diagnosed by evaluation of joint effusion for the presence of increased abundance of neutrophils, although confirmation that the disease is caused by the FCV infection is difficult for any given case. An experimental study showed FCV immunoglobulin and complement within synovial macrophages, which suggests immune complex deposition, even in the absence of clinical signs.[18]

Immune complex, chronic "lymphocytic/plasmacytic" stomatitis or chronic ulceroproliferative stomatitis with prominent gingivitis and faucitis occurs chronically in some cats with previous or ongoing URI, often so severe as to be resistant to management and eventually result in euthanasia.[24] This

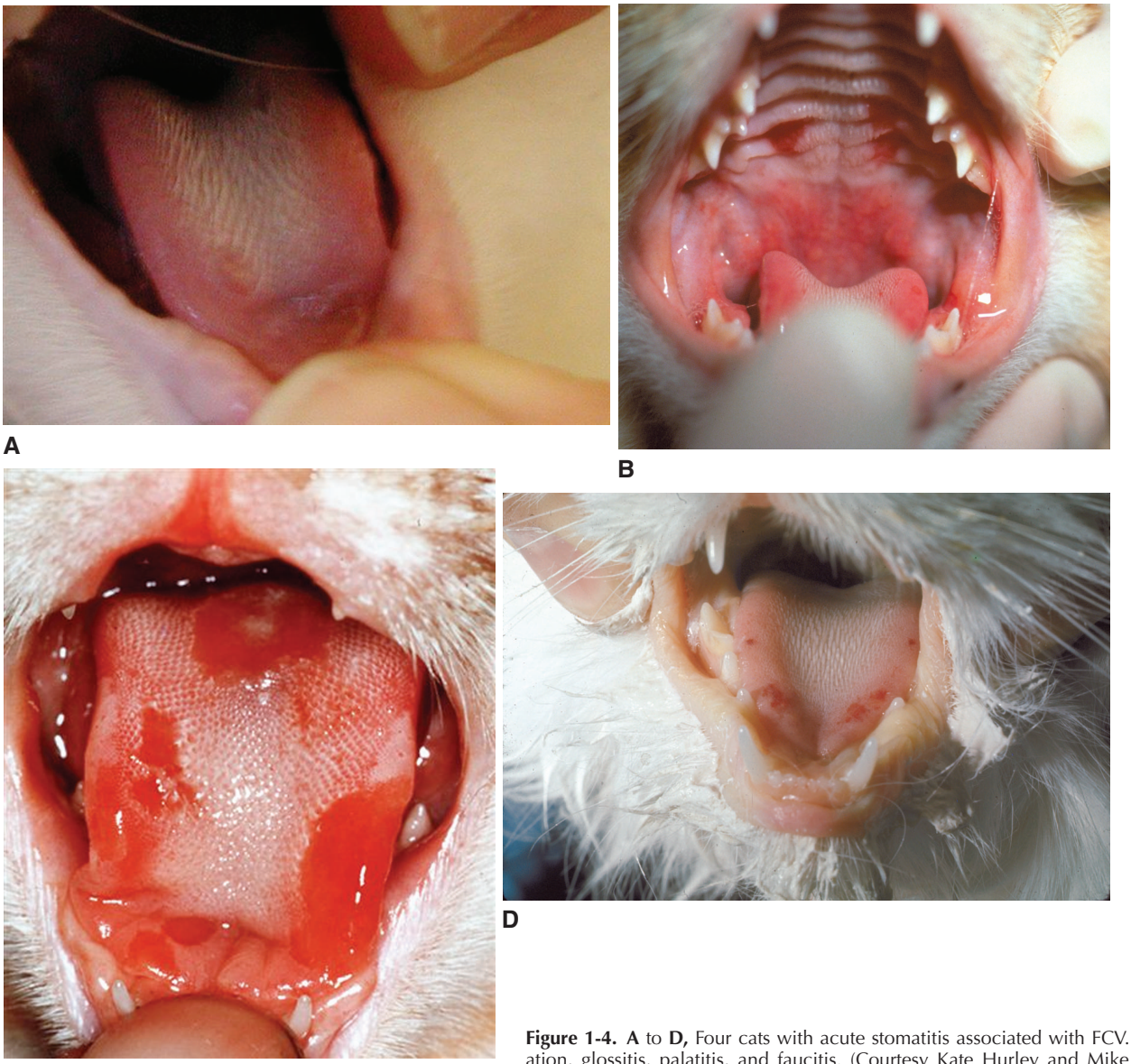

Figure 1-4. A to **D,** Four cats with acute stomatitis associated with FCV. All have ulceration, glossitis, palatitis, and faucitis. (Courtesy Kate Hurley and Mike Bannasch, UC Davis Shelter Medicine Program.)

syndrome should be distinguished from acute stomatitis, which lacks the immune complex deposition and is self-limiting. Affected cats may have ptyalism, halitosis, dysphagia, poor grooming, and weight loss. The gingiva appear swollen and inflamed, sometimes with concurrent faucitis and glossitis (see Chapter 38). Hypergammaglobulinemia may be present,[25] as well as increases in interleukin-2 (IL-2), IL-4, IL-5, IL-6, IL-10, IL-12, and interferon-γ (IFN-γ).[26] The histopathological lesion has plasma cells and lymphocytes predominantly but also may have neutrophils and bacteria because anaerobic oral flora may exacerbate the disease. In one study, 81 per cent of cats with chronic gingivostomatitis were shedding FCV and FHV, compared with only 21 per cent of cats that lacked these clinical signs.[27] Other reports indicate an increased severity of this disease in cats coinfected with feline leukemia virus or feline immunodeficiency virus.[16]

Even more severe disease may occur with cats that have experienced chronic, high-titer FCV infection. Such cats can develop

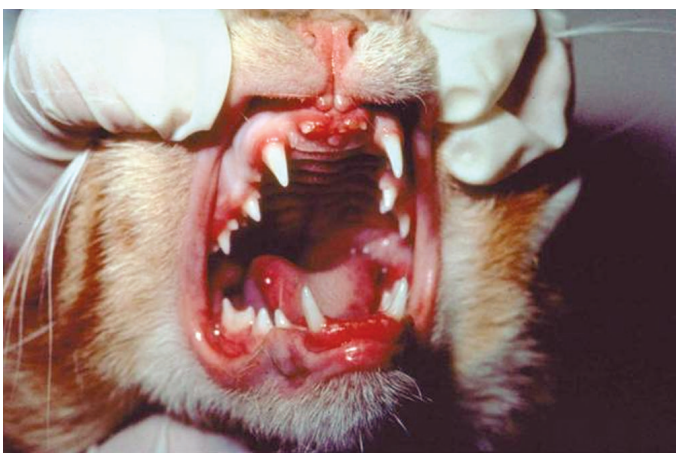

Figure 1-5. Lymphocytic/plasmacytic stomatitis associated with chronic FCV infection. (Courtesy Kate Hurley and Mike Bannasch, UC Davis Shelter Medicine Program.)

progressive immune complex–induced glomerulonephritis, with renal failure characterized by high urine protein concentrations and high urine protein:creatinine ratios. In my experience, such cases occur almost exclusively in overcrowded, multiple-cat households with marginal management.

VIRULENT SYSTEMIC CALICIVIRUS

Recently, a pathogenic series of FCV infections were reported, in which cats developed facial and limb edema comparable to the hemorrhagic fever syndrome observed in RHDV. The virus has been denoted "virulent systemic feline calicivirus" (VS-FCV). This novel pathogen induces up to 67 per cent mortality even in healthy adult cats and has erupted in at least six epidemics since 1998 with epidemiological and clinical similarities to hemorrhagic fever virus epidemics in human beings.[28-30] All outbreaks were characterized by rapid onset and spread, with enigmatic, gradual, or abrupt conclusion.

Cats with VS-FCV infection tend to be very sick, although the case definition is difficult because the original source of the virus in all reported epidemics appears to have been a cat with predominant URI. For several studies, the definition of a case consisted of a cat with consistent exposure history (i.e., from an affected practice or with contact with a confirmed case), clinical signs of VS-FCV (i.e., fever, facial or limb edema, and multiple organ dysfunction), and an FCV strain recovered by culture or PCR with capsid hypervariable region sequences identical to those from a known case strain in the same epidemic.[29,31,32]

VS-FCV infection is distinctive in its clinical severity, tropism for epithelial and endothelial cells, multisystemic attack, induction of systemic vascular compromise, and rate of involvement of visceral organs including lungs, pancreas, and liver with frequent signs of fever, edema, multiple organ failure, hemorrhage, shock, and death. Severely affected cats developed generalized facial and limb swelling, edema consistent with systemic vascular compromise, high fever (39.4° to 42.4° C), multiple organ dysfunction, and sudden death (Figure 1-6). On pathological investigation, affected cats manifested subcutaneous edema, ulceration, and segmental to full-thickness epithelial necrosis of the stratum basale, stratum spinosum, and follicles[31] (Figure 1-7). Many affected cats had pulmonary edema and liver or pancreatic compromise, although VS-FCV was not recovered consistently by culture or PCR from livers of affected cats, in contrast to PCR results from a similar syndrome in lagomorphs caused by RHDV.[1] Immunohistochemical staining with a monoclonal antibody to FCV and transmission electron microscopy documented VS-FCV antigen within affected endothelial and epithelial cells, including within the skin, nasal mucosa, tongue, buccal mucosa, pinna, paw pads, and lungs. Transmission electron microscopy documented viral antigen within endothelial and epithelial cells in affected skin.

The pathogenesis of virulent systemic caliciviral infection is not fully known but appears to be at least partly immune-mediated. This is supported by the reported increased disease severity in older cats,[29] similar to that in RHD, in which young rabbits experience self-limiting diseases, whereas older infected rabbits have almost 100 per cent mortality.[33] Cats infected with VS-FCV may have systemic vascular compromise and hemorrhagic-fever–like signs, in part resulting from viral invasion of epithelium and endothelium, coupled with host cytokine responses.[32] Affected tissues of cats with VS-FCV infection had prominent upregulation in IL-10, TNF-α, and macrophage inflammatory protein-1α (MIP-1α), but no differences compared with control tissues in the cytokines IL-1β, IL-2, IL-4, IL-6, IL-12p40, IL-18, IFN-γ, IFN-α, and regulated on activation, normal T expressed and secreted (RANTES). MIP-1α is secreted by numerous cell types, chemoattractant for macrophages and monocytes, pyrogenic, and a potentiator of IFN-γ production.[34] IL-10 is secreted by T_H2 and macrophages, although it feeds back and inhibits further macrophage cytokine release. In the skin, IL-10 stimulates mast cells and IgA-producing B-cells, and upregulates MHC-II expression. TNF-α is a T_H1 cytokine and may be important in the pathogenesis of VS-FCV because of its ability to increase vascular permeability, stimulate acute phase

Figure 1-6. Cat affected with VS-FCV, showing marked facial edema and crusting of the pinnae. (Courtesy Dr. Kate Hurley and Mike Bannasch, UC Davis Shelter Medicine Program.)

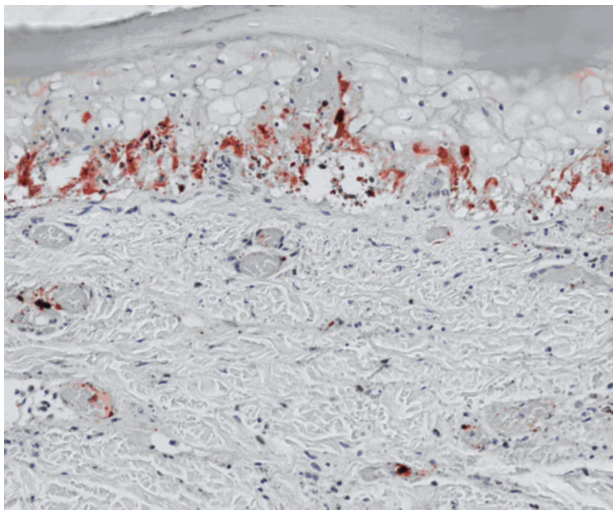

Figure 1-7. Section of feline skin affected with virulent systemic feline calicivirus infection. Strong anticalicivirus immunoreactivity is observed within basal layer of epithelium in an extensive lesion of epithelial necrosis and scattered in endothelial cells of the dermis. (Courtesy Patricia Pesavento, UC Davis California Animal Health and Food Safety Laboratory.)

responses from liver, and induce complement activation, fever, and shock. Overall, the cytokine and published pathology findings suggest immunopathogenic sequelae after direct viral invasion of endothelium and epithelium; in severe, generalized cases this could lead ultimately to systemic vascular compromise, microthrombus formation, disseminated intravascular coagulation, and death. This contrasts with the pathogenesis of other diseases associated with systemic vascular compromise, such as inflammatory vasculitis in Rocky Mountain spotted fever,[35] immune complex vasculitis in feline infectious peritonitis,[36] or direct viral tissue cytotoxicity that leads to edema in rabbit hemorrhagic disease.[37,38]

The rapid emergence of the novel VS-FCV–associated clinical syndrome suggests that new genetic FCV variants could be responsible. If a novel emerging FCV genotype were responsible for the highly virulent phenotype, then all isolates from within an epidemic should be closely related genetically and consistent genetic changes should be detected from VS-FCV strains from among various outbreaks. In the Los Angeles outbreak, all VS-FCV strains obtained from case cats clustered very closely together and contained a characteristic deletion of 3 nucleotides.[29] However, when 235 nucleotide amplicons in the viral capsid hypervariable region from northern and southern California VS-FCV outbreak strains were compared with North Carolina and Florida VS-FCVs, F9 (the vaccine strain), and miscellaneous field strains, this 3 nt deletion was missing in VS-FCVs from other outbreaks.[32] Instead, VS-FCV strains from different regions were scattered among VS-FCV and FCV field strains. A VS-FCV isolate designated FCV-Ari (from northern California) clustered closely with the F9 vaccine.[28] Thus the data show that VS-FCVs are not all members of a single clade; rather, these mutant viruses are emerging from several different lineages intermixed with other field strain FCVs. Researchers studying the RHDV have obtained similar results, in which no specific genetic viral determinants have been related to the emerging rabbit disease. A second plausible mechanism for the emerging disease is that several different mutant viruses may share common pathogenic determinants when they interact with feline cells. Particularly if much of the disease pathogenesis is immune mediated, the initial virus-host interaction could initiate common immune sequelae even if the original viral genotype differed. Novel receptor or other host-virus interactions perhaps could occur as a result of mutated capsid protein structure, particularly targeting epithelial or endothelial cells. The skin's endarterial circulation and unique local immune cell populations (particularly dendritic cells capable of secreting TNF-α) are additional intriguing targets for further evaluation of VS-FCV–host interactions.

DIAGNOSIS OF FELINE CALICIVIRAL DISEASE

Culture

Virus culture can be performed to test for FCV in addition to FHVs, using the same cells and techniques. Samples must be collected and either processed fresh or kept frozen for culture and can include swabs from eyes, nose, and oral cavity, in addition to lungs or any potentially infected tissue, including spleen, lungs, or less frequently liver or other internal organs. Swabs should be maintained in viral transport medium such as Hanks buffered salt solution (Gibco BRL), which often contains antibiotics, so the same swabs are not appropriate for bacterial isolation. FCV is cultured commonly on a confluent monolayer of Crandall-Reese feline kidney (CRFK) cells at 37° C in air with 5 per cent CO_2 in 1:1 Liebovitz L-15 medium and Eagle's minimum essential medium with 10 per cent fetal bovine serum, incorporating antibiotics to minimize problems with contaminating bacteria. Infection is assessed by the presence of characteristic cytopathic effects within 12 to 52 hours; however, care must be taken to distinguish FCV cytopathic effect from that resulting from herpesvirus, which typically occurs later after infection. Herpesvirus-infected cells typically round up and detach diffusely from the tissue culture flask and develop a moth-eaten appearance. Individual cells may appear connected by cytoplasmic streamers or may combine into giant or syncytial cells. In calicivirus infection, the whole monolayer becomes detached and cell clusters appear similar to a bunch of grapes in the tissue culture fluid. Positive culture or PCR results should be attributed as causal to the clinical signs with caution, because cats can be culture-positive in the absence of disease.

PCR and cDNA Sequencing

Because FCV are RNA-viruses, PCR typically is performed after the genome is reverse-transcribed to make copyDNA (cDNA). Reverse-transcription PCR (RT-PCR) can be performed from any potentially infected tissue or from tissue culture fluid. An excellent target is the 235 nucleotide amplicon in the viral capsid hypervariable region.[39] If desired, the products can be sequenced directly to compare with other FCV sequences. For example, comparison of amplicons from Los Angeles (2002 southern California outbreak) to sequences from VS-FCVs from northern California (FCV-Ari strain), North Carolina, and Massachusetts, the vaccine strain F9, and miscellaneous field strains, was important in understanding the molecular epidemiology of emerging VS-FCV strains.

Immunohistochemical Staining

A monoclonal antibody anti-feline calicivirus CV8-1A (c) has been developed to identify FCV in situ (Custom Monoclonals Inc., Sacramento, California), although the full specificity of this product has not been evaluated yet. Formalin-fixed, paraffin-embedded tissues can be sliced into 5-µm sections, mounted on positively charged slides, deparaffinized in xylene, and washed with ethanol. Endogenous peroxidase activity should be quenched with hydrogen peroxide in methanol for 10 minutes, followed by ethanol and water rinses, and antigen retrieval with proteinase K. The primary FCV antibody is diluted in 10 per cent horse serum to a final protein concentration of 0.064 mg/ml and the slides incubated with 100 µl of the diluted monoclonal antibody for 1 hour at room temperature in a humidified chamber. After primary antibody incubation, the slides are rinsed with tris-buffered saline with Tween 20 and labeled with an anti-mouse horseradish peroxidase secondary antibody. When developed with the chromagen, counterstained with hematoxylin, and examined microscopically, this stain can be useful in evaluation of VS-FCV cases and also is helpful in cases of pneumonia.

TREATMENT AND MANAGEMENT

URI is the most common infectious syndrome in shelter animals and many cats harbor clinically silent or subtle FCV

and FHV infections. URI in an individual cat is common and often manageable. However, because URI propagates so readily within shelters, it may be considered a "fatal disease" because of risks to other shelter cats, difficulties managing affected cats, and the likelihood that affected cats will not be adopted. Cats harboring latent or pre-clinical URI often require veterinary care within days of adoption, which incurs cost and frustration by adopters and further erodes public confidence in the shelter, in turn decreasing adoption. URI in cats is the second leading cause of euthanasia in shelters after overcrowding.[40] Shelters manage URI with isolation, vaccination, and antibacterial or antiherpetic treatment (see Chapter 77).

Kittens born to vaccinated or naturally infected queens may have some protection against FCV, but it is minimal. Maternal immunity to protect the kittens can be short-lived, lasting from 3 to 9 weeks. Even cats that have recovered from earlier infections with calicivirus may not be protected if the challenge is with an antigenically dissimilar virus. However, as cats mature to about 3 years of age, their innate protective mechanisms appear to finally develop the capability to defend the cat against calicivirus, and many kittens that appeared chronically infected will finally stop showing clinical signs.

Quarantine is useful for control of FCV in high-density cat populations; many latently infected cats can be identified because the stress of being introduced to the environment often reactivates quiescent infections. However, quarantine cannot control or eradicate URI completely because (1) many cases are due to FHV, (2) cats do shed FCV even without clinical signs, and (3) the virus is so contagious that even a few infected cats slipping through quarantine can introduce infection to many other cats in the population. Nevertheless, if resources allow, severely infected cats should be isolated and treated. Mildly affected cats represent the biggest dilemma: some will stay mildly affected for months and should not remain in isolation that entire time (i.e., they should go to a home, where the low cat density and low stress often encourage recovery). On the other hand, shelter personnel tend not to remove mild cases from adoption (some of which probably are manifesting only vaccine reactions), which ensures that the well cats are exposed. A balanced strategy for URI management is to separate cats into three populations: completely well, adoptable mildly affected, and isolation/treatment. If mildly affected cats are to be adopted, communication and client education must be excellent (see Chapter 77).

Vaccination for FCV does not prevent infection consistently, although in many instances, the vaccine mitigates signs of severe disease.[41] Unfortunately, some of the modified live vaccines induce mild to moderate URI, which is indistinguishable clinically from disease caused by "field strain" pathogens. Subcutaneously administered vaccines can induce oropharyngeal shedding of vaccine-strain virus.[2] Genetic analysis in several studies documented that cats could have URI and vaccine-like FCV isolates (which were consistent with vaccine-induced morbidity), possibly representing vaccine failure.[29,39] A killed virus vaccine is commercially available that will reduce vaccine-associated morbidity. However, this vaccine has disadvantages: (1) the vaccine usually must be given at least 2 times (at least 2 to 4 weeks apart) before effective immunity is produced, (2) the adjuvant may be locally irritating and predispose cats to later vaccine-associated sarcoma, and (3) the cat is *not protected* for 2 weeks or longer after the first vaccination. Advantages include (1) the cat does not experience "mild" infection and (2) false-positive virus culture or PCR tests are far less likely.

Nursing care and maintenance of hydration are the most important components of care for cats with URI. Cats with plugged noses, sore mouths, or any indication of inappetence may need to be encouraged to eat, especially if they are young kittens. To accomplish this, the nose is cleaned gently and warmed all-meat baby food (with no onion powder) is offered. Antibiotics should be reserved for cases with green purulent discharge, a concern of sepsis, or a strong suspicion of secondary bacterial infection (because antibiotic use affects normal flora adversely and promotes antibiotic resistance and susceptibility to further infection).

Cats with immune complex complications of FCV infection require immunosuppressive therapy. Treatment for FCV-induced polyarthritis consists principally of immunosuppressive steroid treatment. Cats that do not begin to show improved clinical signs and resolve acute inflammation may require additional immunosuppression such as azathioprine. This treatment increases the risk of exacerbating frank URI. Treatment for chronic FCV-associated stomatitis is extraordinarily difficult. Recommended options have included broad-spectrum antibiotics with particular efficacy for anaerobic bacteria, dental disinfectant rinses, steroid administration, and full-teeth extractions, but often cases are refractory to treatment, progressive, and severely debilitating. Administration of aggressive immunosuppression must be performed cautiously, especially in cats with both FCV and FHV infection. However, the cat's quality of life with active stomatitis is so poor that the risk of immunosuppression is warranted. Nevertheless, some cases of stomatitis and glomerulonephritis are essentially untreatable.

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Chapter 2

Cutaneous Manifestations of Viral Disease

Joanne K. Mansell and Christine A. Rees

FELINE HERPESVIRUS-1 DERMATITIS
FELINE LEUKEMIA VIRUS
FELINE IMMUNODEFICIENCY VIRUS
FELINE PAPILLOMAVIRUS
FELINE CALICIVIRUS
COWPOX

Two different routes of infection may cause viral lesions in the skin: (1) direct localized inoculation of the skin by virus or (2) cutaneous lesions associated with systemic viral disease. The intact skin is impenetrable to direct viral insult; however, the intact skin can be damaged or penetrated by insect bites, cuts, and foreign body injury, and localized viral inoculation can occur through damaged skin. Systemic disease also can result in cutaneous lesions by localization of virus in the skin during the viremic stage. Currently, a limited number of viral diseases have been described that affect the skin of cats. Cutaneous disease occasionally can occur with calicivirus and feline leukemia virus (FeLV) infection, and are examples of systemic diseases that sometimes can cause skin lesions. Cutaneous lesions also can be caused by the recrudescence of feline herpesvirus-1 (FHV) in the absence of upper respiratory disease. Papillomavirus has been found in association with feline cutaneous fibropapillomas. Orthopoxvirus (cowpox) infection in cats in the Old World is an example of a viral disease that is presumed to occur by direct inoculation at sites of skin damage.

FELINE HERPESVIRUS-1 DERMATITIS

FHV usually is associated with upper respiratory disease and oral ulceration in kittens (see Chapters 38 and 77). As with most herpesviruses, FHV can establish latency in the trigeminal nerve after upper respiratory disease and can recrudesce in times of stress.[1] In cats, conditions of stress include overcrowding, a change of environment, corticosteroids, systemic disease, and pregnancy. FHV can reactivate and cause skin lesions, generally without signs of upper respiratory disease.[2] Skin lesions usually are seen on the haired skin of the nasal planum (Figure 2-1), although they also can occur less frequently on the face, feet, ears, and ventrum. Clinically, the lesions are characterized by ulceration and crusts on the nose that can be persistent and/or recurrent. When a cat has ulcerated skin in these locations, several differential diagnoses must be considered. Feline eosinophilic granuloma, mosquito-bite hypersensitivity (see Chapter 25), and squamous cell carcinoma all are conditions that commonly produce ulcers located on the bridge of the nose or nasal planum. Because the treatment for these conditions varies, and therapies for some of these diseases may be contraindicated in others, the lesions should be biopsied and the tissues submitted for histopathology to differentiate between these conditions definitively.

Microscopically, the skin is characterized by ulceration and necrosis with mixed dermal inflammation that commonly includes numerous eosinophils. Necrosis often destroys the adnexae, and keratin released from ruptured adnexae often is accompanied by eosinophilic infiltration and sometimes by collagen degeneration. The necrosis also can produce small rafts of adnexal epithelial cells surrounded by necrotic debris in the dermis, and amphophilic to glassy intranuclear viral inclusions can be found in the epidermis and adnexal epithelial cells (Figure 2-2). These inclusions can be rare and difficult to find. A careful search must be made because the eosinophilic nature of the inflammation can mimic an allergic skin condition. Immunohistochemistry and polymerase chain reaction (PCR) tests have been used to confirm viral inclusions seen in skin lesions as FHV-1.[3]

Several different therapeutic options have been used against FHV. The most commonly used treatment is L-lysine. Lysine is an essential amino acid that blocks the bioavailability of arginine. Therefore lysine supplementation causes inhibition of herpesvirus replication by lowering the amount of arginine that is present.[4,5] Interferon-alpha (IFN-α) also has been used in the treatment of feline herpesvirus infection. IFN-α is a cytokine with antiviral, antiproliferative, and immunomodulating activity.[6] Low-dose IFN-α (30 units PO q24h) has been used anecdotally in the treatment of FHV dermatitis. No side effects have been reported at this low dosage. Acyclovir is an antiherpesvirus medication used in human medicine. Although acyclovir has been recommended for the treatment of FHV infection, one study demonstrated that acyclovir is ineffective against this virus.[7]

FELINE LEUKEMIA VIRUS

Feline leukemia virus is a retrovirus that causes systemic immunosuppression. FeLV-infected cats can be expected to have secondary skin infections, such as recurrent pyoderma or abscesses. Rarely, primary FeLV viral infection of keratinocytes occurs. FeLV dermatitis results in scaling, crusting,

Figure 2-1. FHV dermatitis. Ulcerative lesions on the haired skin of the nasal planum.

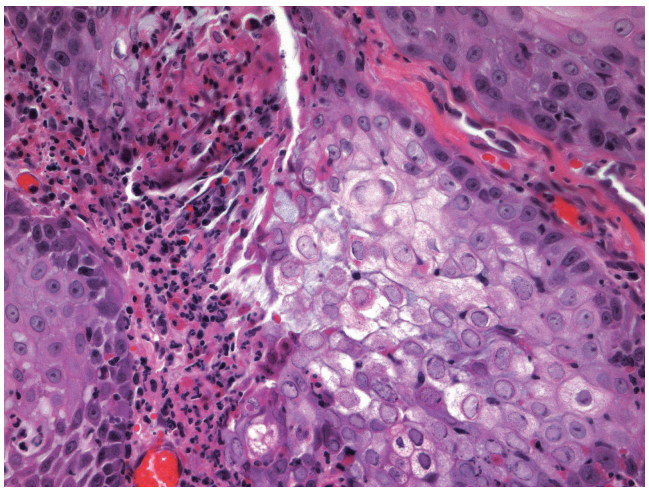

Figure 2-2. FHV dermatitis. A raft of epithelial cells surrounded by necrotic cellular debris. Epithelial cells have enlarged nuclei with pale glassy intranuclear inclusions.

Figure 2-3. FeLV dermatitis. Scaling, crusting, and alopecia of the head and neck.

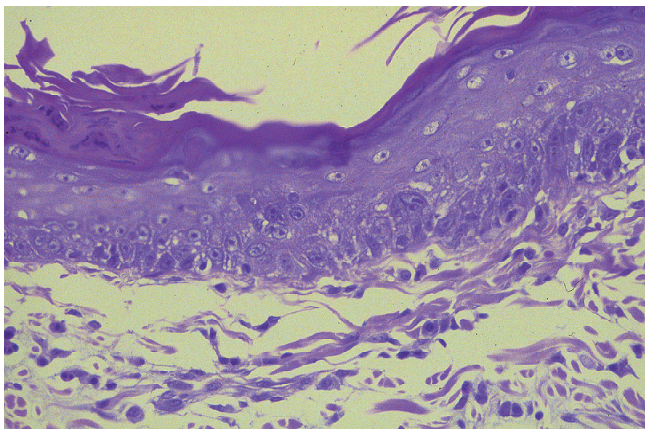

Figure 2-4. Giant cell dermatosis in an FeLV-positive cat. Syncytial cells involving keratinocytes in the epidermis.

and alopecia, primarily of the head and face, with rare generalized distribution (Figure 2-3). This condition has been named *giant-cell dermatosis in FeLV-positive cats.*[8] Histologically, syncytial cells (giant cells) can be seen in the epithelial cells of the epidermis and follicular epithelium, with dyskeratosis, pustules, and ulcers (Figure 2-4). FeLV antigen can be demonstrated in the giant cells and adjacent keratinocytes by immunohistochemistry.

Multiple cutaneous keratin horns also have been associated with FeLV infection (Figure 2-5). C-type viral particles were identified in keratinocytes of the footpad, and FeLV was isolated from footpads in some of the cats.[9,10]

No treatment eliminates FeLV infection. Zidovudine (AZT) given at 5 mg/kg PO q8h may reduce virus load and help improve clinical signs. Because AZT may cause bone marrow suppression in cats, hemograms should be monitored frequently during the course of therapy. Recombinant feline interferon omega (rFeIFN-Ω), administered subcutaneously, improved survival time of FeLV- and feline immunodeficiency virus (FIV)–infected cats in one recent study. However, this agent is not commercially available at this time.

FELINE IMMUNODEFICIENCY VIRUS

Feline immunodeficiency virus is a lentivirus that also causes immunosuppression. Similar to FeLV, FIV-associated skin disease usually is secondary to systemic immunosuppression. Bacterial dermatitis, generalized demodex infection, notoedric mange, atypical mycobacteriosis, subcutaneous abscesses and cellulitis, and cowpox infection all are skin diseases that have been reported to be more common in FIV-infected cats than in uninfected cats.[12,13] No treatment exists for treating FIV infections other than addressing the secondary infections or infestations that occur. Antiviral or immunomodulatory therapy, as described for FeLV, may help to reduce immunosuppression and improve the rate of recovery from these infections.

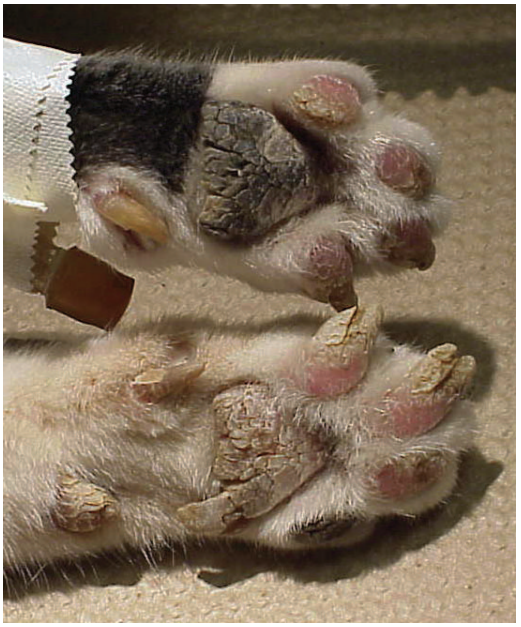

Figure 2-5. Multiple cutaneous horns on the footpads associated with FeLV.

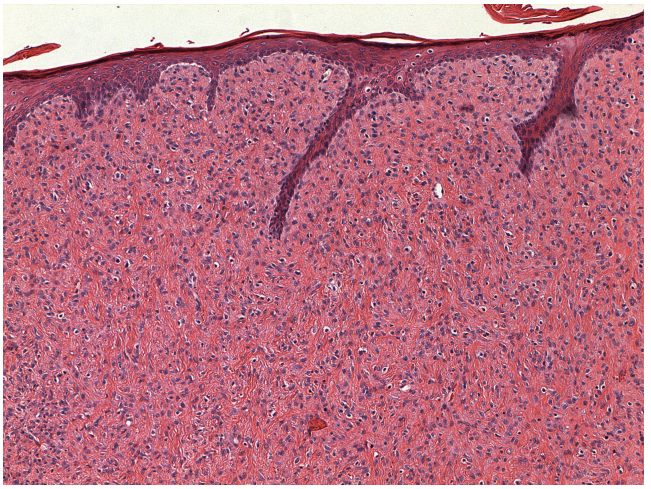

Figure 2-6. Feline sarcoid. Haphazardly arranged spindle cells separated by collagenous stroma. The overlying epidermis has long rete ridges.

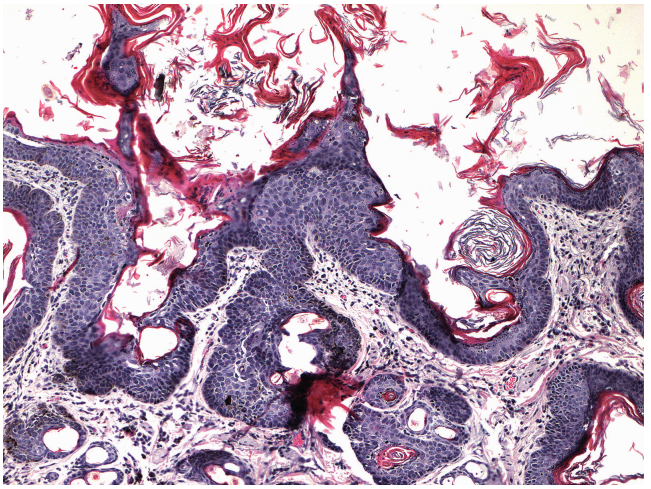

Figure 2-7. Multicentric squamous cell carcinoma in situ. The epidermis and superficial follicular epithelium are thickened by disorganized dysplastic and neoplastic keratinocytes.

FELINE PAPILLOMAVIRUS

Feline cutaneous fibropapillomas are cutaneous masses that occur most commonly in young cats and have histological features similar to equine sarcoids.[14] Immunohistochemical staining has failed to detect papillomavirus antigens; however, papillomavirus-DNA has been detected by PCR, DNA sequencing, and nonradioactive in situ hybridization in the mesenchymal cells of the tumor, which suggests a causal relationship. Because the histological features and pathogenesis are so similar to equine sarcoids, the suggestion has been made that these lesions should be renamed *feline sarcoids.*[15] Feline fibropapillomas are uncommon and occur primarily on the head, neck, and digits. The majority of reported cases occur in cats less than 5 years old.

Histologically, the tumors are characterized by a dermal fibroblastic spindle cell proliferation with mild to moderate epithelial hyperplasia and rete ridges in the overlying epidermis (Figure 2-6). Neoplastic spindle cells have oval to elongated nuclei and scant eosinophilic cytoplasm, with a low mitotic rate, and are arranged haphazardly separated by variable amounts of collagenous stroma. Similar to equine sarcoids, the spindle cells are multifocally oriented perpendicularly to the epidermis. In the limited number of cases that have been reported, the prognosis is similar to equine sarcoids in that local recurrence after surgical excision is common, but metastasis does not occur.

Papillomavirus infection also has been associated with *multicentric squamous cell carcinoma in situ.*[16] This type of squamous cell carcinoma is confined by the basement membrane and usually is multicentric in the skin. The condition usually occurs in middle-aged or older cats and presents as single or multiple irregular, elevated plaques on haired pigmented skin. Histologically the epidermis and superficial follicular epithelium, primarily the spinous and basal layers, are thickened and disorganized by neoplastic keratinocytes (Figure 2-7). Mitotic figures and keratin pearls may be seen.

Finally, papillomavirus antigen has been found in nonneoplastic hyperplastic cutaneous plaques in immunosuppressed cats (*cutaneous hyperplastic plaques*).[17] Plaques have been reported on the skin and tongue of cats and appear as rough, raised, pigmented or unpigmented, scaly, greasy plaques 3 to 5 mm in diameter. Raised plaques of hyperplastic keratinocytes with an abrupt junction between the plaque and the normal tissue characterize the lesions histologically. The squamous epithelium has thickened suprabasilar layers and a prominent stratum granulosum. In the granular layer, koilocytes, altered keratinocytes characterized by pale cytoplasm and vesicular nuclei, and prominent pleomorphic keratohyalin cytoplasmic granules are present. The cutaneous plaques may be pigmented and hyperkeratotic. Papillomavirus antigen can be demonstrated in the nuclei of the koilocytes using immunohistochemical staining.

Treatment of skin lesions associated with feline papillomavirus usually is not practical because multiple skin lesions are present and the recurrence rate is high. A preliminary study suggests that beta radiation therapy (strontium-90 plesiotherapy) may be effective in treatment of early lesions.[18]

FELINE CALICIVIRUS

Infection with feline calicivirus (FCV) is common, especially in multiple cat settings such as shelters and catteries (see Chapters 1, 38, and 77). Clinical signs of acute disease include oral ulceration, ocular and nasal discharge, conjunctivitis, fever, and rarely, lameness. After recovery from the acute disease, it has been estimated that up to 25 per cent of cats shed virus persistently from the oropharynx. Most of these cats are asymptomatic; however, they may be the source of infection for other cats. Some of these infected cats develop chronic effects of calicivirus carriage such as lymphocytic/plasmacytic gingivostomatitis.[19]

Infection with FCV rarely is fatal unless the affected animals are young kittens with upper respiratory disease. Recently, however, a virulent systemic form of FCV (hemorrhagic calicivirus) has produced outbreaks of disease in group-housed cats with high mortality rates ranging from 33 to 60 per cent[20-22] (see Chapter 1). Many affected cats were healthy adults that had been vaccinated previously against calicivirus. Clinical signs in cats with virulent systemic FCV are fever, anorexia, icterus, marked subcutaneous edema of the limbs and face, oral ulceration, alopecia, crusting, and ulceration of the nose, lips, pinnae, and feet. Some cats also had conjunctivitis, pulmonary edema, bronchointerstitial pneumonia, pleural effusion, and foci of fat necrosis in the peripancreatic fat and omentum with splenic and lymphoid necrosis.

Histologically, the ulcerations of the nose, mouth, pinnae, and paw pads were characterized by segmental epithelial necrosis of the stratum basale and stratum spinosum with involvement of the follicular epithelium and the epidermis. Chronic lesions exhibit full thickness necrosis of epithelium with ballooning degeneration in the superficial epidermis.[20] FCV antigen was identified by immunohistochemistry in epithelial and endothelial cells of affected areas of skin, nasal mucosa, tongue, mouth, ears, paw pads, lung, and pancreas; virus particles compatible with FCV were identified by electron microscopy. The pathogenesis of the virulent strain of FCV has not been fully characterized; however, FCV is a RNA virus prone to high mutation rates. Calicivirus has been shown to be able to mutate and cause epidemics in rabbits, as demonstrated by rabbit hemorrhagic disease. Mutation of FCV presumably has resulted similarly in a highly virulent strain of FCV, which has led to high mortality rates in adult cats.

No treatment exists for FCV other than symptomatic treatment. Any secondary bacterial infections that occur should be treated.[23] A full discussion of virulent systemic feline calicivirus infection may be found in Chapter 1.

COWPOX

Cowpox is in the *Orthopoxvirus* genus. In Europe and Great Britain, the reservoir for cowpox is small wild rodents, such as voles and mice.[24] Cats may become infected as a result of their hunting activities, and cowpox lesions in cats sometimes are referred to as "catpox." Cutaneous lesions associated with cowpox infection have been documented in Europe and Great Britain but have not been seen in the United States.[25] Cats infected with cowpox develop cutaneous lesions on the face, neck, forelimbs, and paws. The primary lesion usually is single and nodular and can progress to an ulcerated plaque or papule. Secondary lesions, which may be multiple, develop 4 to 16 days after the primary lesion. Cats occasionally have been shown to transmit cowpox infection to human beings; therefore cats suspected of having cowpox should be handled cautiously.[26,27] Occasionally cowpox lesions can be found in the respiratory system, and clinical signs of upper respiratory disease may be present in these cats.[25,28] Mild systemic illness and concurrent oral lesions have been reported occasionally.[29] Cowpox rarely is fatal unless the cat is immunosuppressed with concurrent FIV infection.

Histologically, cowpox lesions are characterized by focal ulceration of the epidermis and marked inflammation in the dermis, usually composed of neutrophils and eosinophils. Eosinophilic cytoplasmic inclusions are present in the epidermis at the margins of the ulceration and in follicular and sebaceous epithelium. Cowpox antigen can be detected by immunohistochemistry, PCR, and viral isolation, and characteristic virions can be identified by electron microscopy.

No specific antiviral therapy is available to treat feline cowpox infections. Treatment consists of supportive care and systemic antibiotics if a secondary infection is present. Treatment with glucocorticoids is contraindicated. Environmental treatment with hypochlorite-containing solutions is recommended.[29]

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Chapter 3

INFECTIOUS UVEITIS

Cynthia C. Powell and Michael R. Lappin

Uveal inflammation can result from a variety of causes, such as trauma, infections, neoplasia, and immune-mediated diseases.[1,2] In some cases of uveitis, the inflammatory reaction has no known primary cause and therefore is suspected to be an autoimmune disease. Uveitis is one of the most important groups of ocular disease in cats. It may be the first indication of a serious or life-threatening systemic disease, and the small size and close proximity of all intraocular structures make early recognition and treatment of uveitis imperative to avoid sight-threatening consequences.

ANATOMICAL CLASSIFICATION

Anterior uveitis or iridocyclitis involves inflammation of the iris and ciliary body. Although iritis implies inflammation of the iris only, it often is used synonymously with anterior uveitis. Intermediate uveitis, also referred to as pars planitis, involves predominantly the posterior portion of the ciliary body, the pars plana**.** Strictly speaking, posterior uveitis is inflammation of the choroid (choroiditis), but because the retina usually is affected concurrently, chorioretinitis is a more accurate term. Because the anterior and posterior uveal tissues are parts of a continuum, inflammation commonly occurs in both simultaneously. Panuveitis is the term used when the entire uveal tract is inflamed.

CAUSES

Many exogenous and endogenous causes of uveitis exist in cats. Most exogenous causes are from trauma to the eye, including blunt, penetrating, and surgical trauma that may or may not include infection or corneal ulceration. Endogenous uveitis may be parasitic, infectious, neoplastic, immune-mediated, or idiopathic. Infectious agents that have been associated with development of uveitis in cats can be found in Table 3-1. Between 25[3] and 90 per cent[4] of cases of uveitis in cats have been reported to be associated with clinical or serological evidence of infectious disease. The most common infectious diseases associated with uveitis are toxoplasmosis, feline infectious peritonitis (FIP), feline immunodeficiency virus (FIV), and feline leukemia virus (FeLV).

PATHOGENESIS

As with other tissues, intraocular inflammation is initiated by local tissue injury (e.g., trauma, infectious agent, antigen challenge). Tissue factors and chemoattractants are released from damaged tissue and microorganisms; vasodilation and changes in vascular permeability follow. These changes indicate disruption of the blood-ocular barrier. Inflammatory mediators, released by damaged tissue cells, cause leukocyte activation and migration. Because the globe has no lymphatic drainage, antigens from degraded organisms are transported to the spleen or other lymphoid tissue via the venous system to activate antigen-specific T and B lymphocytes. Immunocompetent T and B lymphocytes then migrate back to the eye and reside in the uvea.[5] Factors believed to help stop the immune response include elimination of the inciting antigen and production of inhibitory cytokines by T and B lymphocytes.[6] If the inciting antigen cannot be removed completely, as in autoimmune disease, chronic inflammation results. Some proposed mechanisms that contribute to development of autoimmune uveitis include (1) abnormal induction of tolerance to autoantigens, (2) release of normally sequestered autoantigens resulting from trauma or infection, (3) molecular mimicry (homology between pathogens and host tissue antigens), and (4) alteration of autoantigen structure resulting from tissue injury or inflammation.[5,7,8] Because uvea contains immunocompetent lymphocytes, chronic or recurrent inflammation also could result from specific or nonspecific activation of lymphocytes by non-self antigens.[9] The clinician must impress upon the client that even with an exhaustive diagnostic evaluation, a specific cause for uveitis may not be found. The client should understand that, regardless of the inciting cause, uveitis may become chronic, treatment may be palliative, and adverse sequelae are common.

Table 3-1 | **Infectious Causes of Uveitis in Cats**

BACTERIAL	VIRAL	MYCOTIC	PARASITIC
Mycobacterium spp.	FeLV	*Cryptococcus neoformans*	*Toxoplasma gondii*
Ehrlichia spp.	FIP	*Blastomyces dermatitidis*	Ophthalmomyiasis
Bartonella spp.	FIV	*Histoplasma capsulatum*	*Cuterebra* spp.
		Coccidioides immitis	Metastrongylus
		Candida albicans	

From Powell CC, Lappin MR: Causes of feline uveitis. Compend Contin Educ Pract Vet 23(2):128-141, 2001.

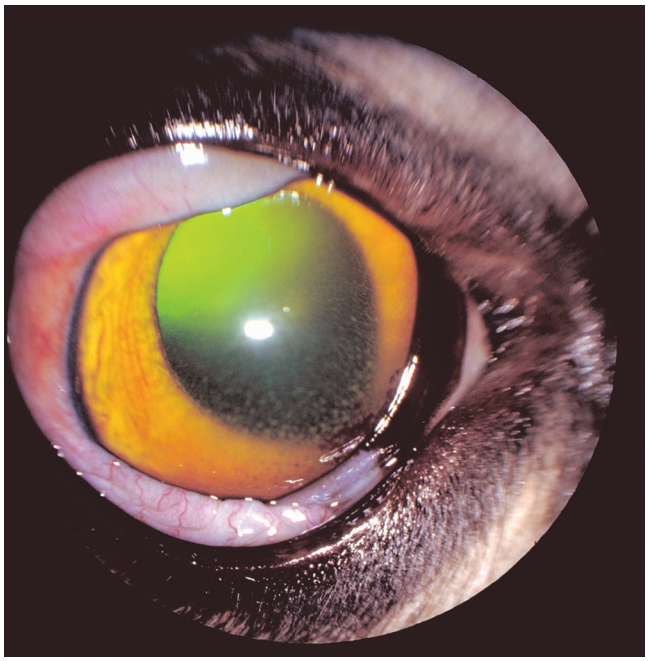

Figure 3-1. Keratic precipitates (KPs), which consist primarily of mononuclear cells, can be seen adhering to the corneal endothelium. Thermal convection currents within the eye cause KPs to be deposited primarily on the ventral half of the cornea. The presence of KPs indicates recent or active anterior uveitis.

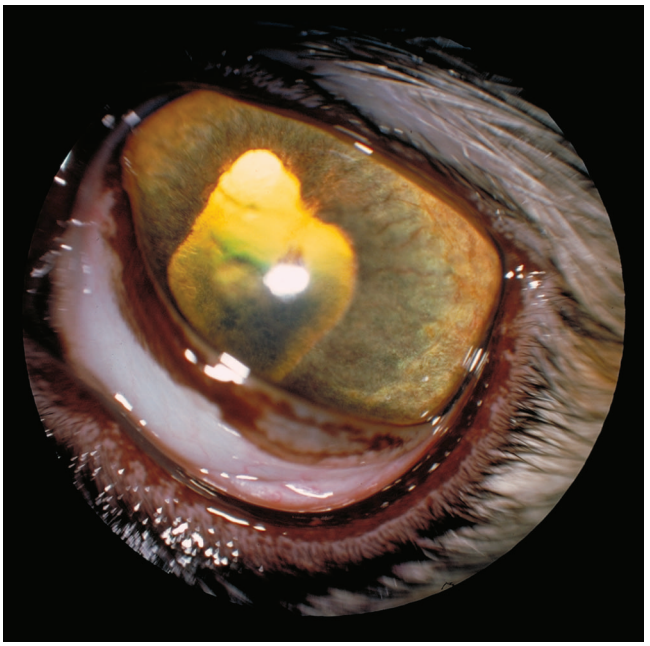

Figure 3-2. Posterior synechiae (adhesions of the iris to the lens capsule) have caused an abnormal shape to the pupil. Posterior synechiae are an indication of previous or active anterior uveitis.

CLINICAL FEATURES

Variations in clinical appearance of uveitis depend on location, duration, and severity. Ocular pain, manifested by photophobia, blepharospasm, enophthalmos, elevation of the third eyelid, and/or epiphora, is common with acute anterior uveitis but may be absent when chronic. Reddened sclera, caused by injection of conjunctival and episcleral vessels, and aqueous flare are the hallmarks of anterior uveitis. Aqueous flare is caused by increased protein concentration in the aqueous humor and is secondary to disruption of the blood-ocular barrier. Light passing through the anterior chamber is scattered in aqueous flare, and if severe, the aqueous humor appears cloudy. Corneal edema can result from the effects of inflammation on the corneal endothelium. As edema increases, the cornea becomes increasingly opaque and blue. Inflammatory cells in the aqueous humor may be deposited on the internal surface of the corneal endothelium as keratic precipitates (KPs). Normal convection currents in the aqueous humor cause KPs to be located primarily on the ventral half of the cornea. Keratic precipitates vary in size. Larger KPs are seen more often with granulomatous inflammatory processes associated with diseases such as FIP and toxoplasmosis (Figure 3-1).

The iris undergoes many changes with anterior uveitis. Inflammatory mediators, in particular prostaglandins, cause *miosis* by a direct effect on the iris sphincter. Very mild miosis is difficult to detect, so its absence should not be used to rule out uveitis. Iritis, manifested by iris vasodilation and increased iris vessel permeability, often causes a subtle to pronounced iris color change. On close examination, dilated iris vessels may be obvious, and the iris may appear swollen and have a thin coat of fibrin and cells giving it a velvet-like texture. As anterior uveitis becomes more chronic, the pupil margin may begin to form posterior synechiae (adhesions to the anterior lens capsule), which give the pupil an irregular shape and impair its ability to respond to light or dilating agents (Figure 3-2). If extensive posterior synechiae develop, aqueous humor cannot move from the posterior chamber to the anterior chamber. Aqueous humor then accumulates behind the iris and causes it to billow forward, a condition known as iris bombé. Because access to the anterior chamber is required for aqueous humor to reach the filtration angle, iris bombé is associated with increasing intraocular pressure and glaucoma. Peripheral anterior synechiae (adhesions of the peripheral iris to the cornea) can form with anterior uveitis as a result of iris bombé or secondary to iris swelling and inflammation. Inflammatory cells, iris swelling, and anterior synechiae also can impair aqueous outflow and contribute to the development of secondary glaucoma.

Aqueous humor formation is impaired when the ciliary body is inflamed. Thus anterior uveitis causes low intraocular pressure unless complicated by secondary glaucoma. Inflammation also causes ciliary muscle spasm, a major contributor to ocular pain. Accumulation of inflammatory cells in the peripheral anterior vitreous is referred to as pars planitis or intermediate uveitis. Because of its peripheral location, pars planitis often is not apparent without dilating the pupil.

Posterior uveitis is inflammation of the posterior uvea or choroid. Because of their close apposition, retinal inflammation often accompanies inflammation of the choroid, which creates chorioretinitis. Changes in the ocular fundus secondary to chorioretinitis are related to the breakdown of the blood-ocular barrier, located at the retinal blood vessels and the retinal pigment epithelium. Increased permeability of these barriers allows components of the blood to accumulate within and between the choroid and retina. Migration of inflammatory cells to the area of inflammation also occurs. Clinically, retinal and subretinal fluid exudes, and hemorrhage can be detected. Because the retina and subretinal space overlie the tapetum, tapetal reflectivity is diminished or obscured by areas of active chorioretinitis (Figure 3-3). Severe chorioretinitis can lead to partial or complete retinal detachment and decreased vision or blindness. Inflammation of both the anterior and posterior uvea is termed endophthalmitis.

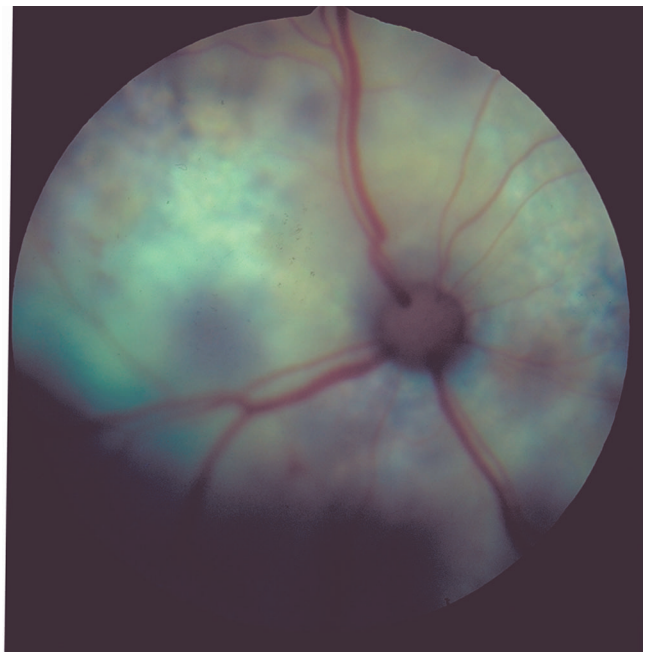

Figure 3-3. Active chorioretinitis in a cat with disseminated toxoplasmosis. Note the mottled, dull appearance of the tapetum. Retinal detachment also is present.

DIAGNOSIS OF INFECTIOUS CAUSES OF UVEITIS

The connection between uveitis and infectious disease can be difficult to make. The causes of uveitis generally cannot be differentiated by the clinical appearance. In addition to a complete physical examination, a complete blood count, urinalysis, and a serum biochemical panel in addition to ancillary diagnostic tests such as serology, aqueous or vitreous humor analysis, and histopathology often are needed to arrive at a specific diagnosis. Ocular fluids can be used for cytology, culture and sensitivity, polymerase chain reaction, and determination of antibody content.

Anterior Chamber Paracentesis

General anesthesia is recommended for anterior chamber paracentesis. To perform paracentesis, a 25-, 27-, or 30-gauge needle on a 1- or 3-ml syringe; small rat-toothed forceps; adequate lighting; and magnification are needed. The bulbar conjunctiva and cornea are flushed gently with a 1:20 povidone-iodine and sterile saline solution. Povidone-iodine soap should not be used because it irritates the cornea and conjunctiva. The globe should be grasped with forceps at the dorsolateral limbus. The needle should enter the eye at the limbus and parallel to the iris plane. The globe will be most stable if the needle enters the eye immediately adjacent to the hold of the forceps. Care should be taken to keep the needle bevel up and the tip away from the iris and lens (Figure 3-4). Up to 0.3 ml of aqueous humor usually can be removed slowly without collapsing the anterior chamber. After withdrawing the needle, gentle pressure is applied to the centesis site using a moistened cotton swab. Samples of aqueous humor can be dropped directly onto a swab for culture and sensitivity, or stored in a sterile container (such as a red top tube) for antigen, DNA, or antibody measurement techniques. Cytological examination is best performed on samples stored in a 1.5-ml blood collection tube that contains ethylenediaminetetraacetic acid (EDTA), concentrated by centrifugation, and stained with DifQuick or Wright's stain. Substrate requirements for PCR and real time-PCR (RT-PCR) assays vary by the assay; many can be performed on frozen samples. Clinicians should contact the appropriate laboratory for transport instructions. Indications for aqueous humor paracentesis are found in Table 3-2. Mild hyphema is the most common complication of aqueous humor paracentesis. Serious complications are rare if care is taken to avoid inadvertent contact with the iris or lens, if no more than

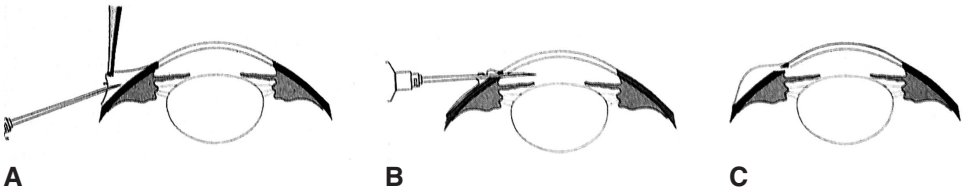

Figure 3-4. Anterior chamber paracentesis. **A,** The needle is tunneled beneath conjunctiva to the limbus. **B,** The needle enters the eye at the limbus with the bevel up and positioned parallel to the iris. **C,** After the needle is withdrawn, leakage of aqueous humor from the entrance site is common but can be controlled with gentle pressure from a cotton-tipped applicator.

Table 3-2 | **Diagnostic Tests for Ocular Fluids**

DIAGNOSIS	AQUEOUS HUMOR	VITREOUS HUMOR
Toxoplasma gondii	IgM, IgG (ELISA) PCR	
FIP, FIV	PCR	PCR
FeLV/Lymphoma	Cytology PCR	Cytology PCR
Bartonella henselae	Culture PCR	
Cryptococcus neoformans	Cytology, culture antigen (latex agglutination or ELISA)	Cytology, culture antigen (latex agglutination or ELISA)

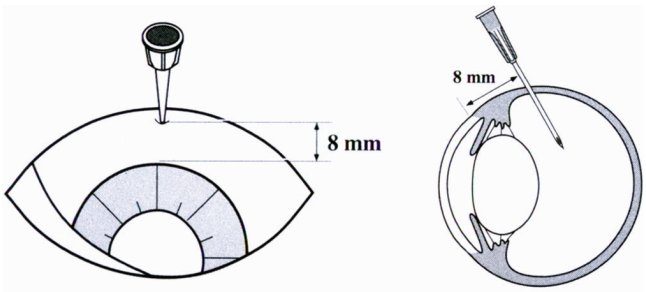

Figure 3-5. Posterior segment (vitreous) paracentesis. **A,** The needle enters the eye at the pars plana, approximately 7 to 8 mm behind the dorsolateral limbus. **B,** The needle is directed towards the middle of the vitreous so that the lens is avoided, or the needle is directed towards a targeted lesion such as a mass or exudate using direct visualization or ultrasound guidance.

0.3 ml of fluid is removed, and if aqueous humor is aspirated slowly.

Vitreous Paracentesis

Vitreous paracentesis should be considered when other methods of diagnosis have been unrewarding and a large vitreous mass or subretinal exudate can be found on ophthalmoscopy or ultrasonography. However, vitreous paracentesis generally is reserved for blind or nearly blind eyes because of the potential for causing severe ocular hemorrhage, retinal tear, and retinal detachment. General anesthesia is recommended. Before aspiration, the bulbar conjunctiva is cleaned gently with 1:20 povidone-iodine and sterile saline solution to remove all mucus and debris. The dorsolateral globe is grasped 6 to 7 mm behind the limbus with small, toothed forceps. Vitreous is viscous and can be difficult to aspirate, so a 3-ml syringe is needed for adequate suction. Aspiration through a 25-gauge needle can be attempted first, but a 22-gauge needle often is needed to obtain a sufficient sample for analysis. The needle should be aimed toward the center of the globe and should be introduced into the eye 7 to 9 mm posterior to the limbus, adjacent to the forceps for maximal stabilization (Figure 3-5). If a mass is present, the needle can be guided by ultrasound into the mass for aspiration. If the ocular media are clear, the needle can be guided visually with use of indirect ophthalmoscopy. Care should be taken not to advance the needle into the opposite retina and choroid. Slightly altering the needle position may help if aspirating fluid is difficult. If bacterial endophthalmitis is suspected and a vitreous injection of antibiotic is planned, the syringe should be removed and the needle left in place for injection. Vitreous samples should be handled the same as aqueous humor samples for culture, cytology, PCR assays, or RT-PCR assays (see Table 3-2).

GENERAL PRINCIPLES OF TREATMENT FOR UVEITIS

The primary treatment goals for uveitis are to stop inflammation, prevent or control the complications caused by inflammation, and relieve pain. Specific and nonspecific therapies are involved in treatment of uveitis. Specific therapies are used for infectious agents (e.g., bacteria, protozoans, fungi) or other contributors to inflammation (e.g., foreign body, corneal ulcer, luxated lens) identified through the examination and diagnostic evaluation. Nonspecific therapy includes decreasing the ocular inflammatory response with antiinflammatory drugs, mydriasis to prevent synechia formation, and cycloplegia to decrease pain. Glaucoma therapy also is instituted when evidence exists of decreased aqueous humor outflow. Therapy for specific agents causing uveitis is discussed under their individual headings.

Nonspecific Therapy for Uveitis

Antiinflammatory therapy is critical in the treatment of uveitis regardless of the cause. Failure to control inflammation can lead to posterior synechiae, glaucoma, cataracts, retinal detachment, vitreous degeneration, optic nerve atrophy, and retinal degeneration. Glucocorticoids and nonsteroidal antiinflammatory drugs (NSAIDs) are used commonly to control inflammation. Glucocorticoids (GC) can be administered topically, subconjunctivally, or systemically. Anterior uveitis usually is treated topically[10] a minimum of every 4 to 6 hours and as frequently as every 2 hours, depending on the severity of inflammation. Aggressive treatment is continued until the inflammation is controlled, and then the frequency of administration should be tapered slowly. If inflammation is not controlled, or if frequent treatments are not possible, supplementation with oral GC should be considered. Topical preparations with the best potency and corneal penetration are prednisolone acetate suspension (1 per cent), and dexamethasone solution (0.1 per cent) or ointment (0.05 per cent).[11] Topical GC are contraindicated in the presence of corneal ulceration because they inhibit wound healing and augment collagenase activity in the cornea.[12] Systemic administration of GC has minimal corneal effects unless the cornea is heavily vascularized; therefore they can be administered if concurrent corneal ulceration and anterior uveitis exist.[13]

Ocular release of prostaglandins can cause disruption of the blood-ocular barrier and uveitis. NSAIDs decrease inflammation by inhibiting cyclo-oxygenase, which results in decreased production of prostaglandins. NSAIDs, unlike GC, do not inhibit the lipoxygenase inflammatory pathway, and little information exists regarding their use for treatment of uveits in cats. Therefore use of NSAIDs should be considered primarily when GC are contraindicated. Frequently used topical ophthalmic NSAIDs include diclofenac 0.1 per cent, flurbiprofen 0.03 per cent, suprofen 1 per cent, and ketorolac 0.5 per cent. Ocular hemorrhage caused by platelet aggregation inhibition[12,14] can be

Table 3-3 | **Drugs Commonly Used to Treat Uveitis in Cats**

TOPICAL	DOSAGE
CORTICOSTEROID	
Prednisolone acetate 1% (suspension)	q1-12h
Dexamethasone sodium phosphate 0.1% (solution), 0.05% (ointment)	q1-12h
NSAID	
Diclofenac 0.1% (solution)	q6-12h
Flurbiprofen 0.03% (solution)	q6-12h
Suprofen 1% (solution)	q6-12h
Ketorolac 0.5% (solution)	q6-12h
MYDRIATIC/CYCLOPLEGIC (PARASYMPATHOLYTIC)	
Atropine sulfate 0.5%, 1% (solution and ointment)	q8-24h
Tropicamide 0.5%, 1% (solution)	q6-12h
MYDRIATIC (SYMPATHOMIMETIC) IN CONJUNCTION WITH PARASYMPATHOLYTIC	
Phenylephrine hydrochloride 2.5%, 10% (solution)	
ORAL	**DOSAGE**
CORTICOSTEROID	
Prednisolone, 5-mg tablet or prednisone 5-mg, 20-mg tablet	0.5 to 2.2 mg/kg q12-24h (higher dosages for initial therapy of severe inflammation)
NSAID	
Acetylsalicylic acid, 80-mg tablet	80 mg q48-72h
Ketoprofen, 12.5-mg tablet	2 mg/kg initially, 1 mg/kg daily maintenance
Phenylbutazone, 100-mg tablet	5 to 7 mg/kg q12-24h (recommended not to exceed 5 days)
Meloxicam, 1.5 mg/ml	0.025 mg/kg two to three times per week (not to exceed 0.1 mg maximal dose/cat)
SUBCONJUNCTIVAL	**DOSAGE**
LONG-ACTING CORTICOSTEROID	
Methylprednisolone acetate	4 mg/eye
Betamethasone	0.75 mg/eye
Triamcinolone	4 mg/eye

a potential complication of their use. Topical NSAIDs may complicate bacterial corneal infections and are not recommended when corneal infection is present.[12,15]

Systemic drug therapy is necessary to treat posterior uveitis, because therapeutic concentrations cannot be attained in the retina and choroid with topical drugs. Because GC suppress the immune response, they should be used with caution (if at all) when infection is suspected, especially if given systemically. If they are used during infection, concurrent treatment with an effective antimicrobial is essential. Drugs, dosages, and routes of GC administration can be found in Table 3-3. Use of systemic NSAIDs in cats has been associated with potentially serious side effects, including bone marrow suppression, gastrointestinal ulceration, hemorrhage, vomiting, and diarrhea.[16] Aspirin, phenylbutazone, ketoprofen, and meloxicam can be used systemically in cats with careful attention to dose, frequency of administration, and possible side effects.[17,18] The course of phenylbutazone therapy should be kept as short as possible, preferably not exceeding 5 days at higher dosages, and the drug should be withheld if inappetence or depression develops.[16] Duodenal perforation in a cat following treatment with oral carprofen has been reported.[19] Other reports indicate that carprofen can be administered safely to cats as a postoperative analgesic.[20]

Subconjunctival GC have been used to supplement topical or systemic GC therapy in cases of severe ocular inflammation or in patients in which frequent topical treatment is not possible.[10] Most subconjunctival preparations used are long-acting, and give a constant source of drug release for a 2- to 4-week period. A disadvantage to their use is the inability to withdraw the medication if complications arise. Drugs injected subconjunctivally enter the eye through the cornea, by leakage through the injection site, and through the sclera.[15] Subconjunctival GC are contraindicated with active corneal ulceration. Topical and subconjunctival GC use also may result in reactivation of feline herpesvirus-1 in carrier cats with previous episodes of viral keratitis or conjunctivitis.[21] Administration of subconjunctival GC to cats suspected to have recurrent feline herpesvirus ocular disease is not recommended.

Cycloplegics relieve pain associated with anterior uveitis by relaxing the ciliary body and iris muscle spasm. Mydriatics can prevent or break down posterior synechiae by dilation of the pupil and reduction of iris-lens contact. Cycloplegia and mydriasis can be accomplished by using a parasympatholytic agent. Topical 1 per cent atropine sulfate ointment is used most commonly, because the ocular solution is more likely to reach the mouth via the nasolacrimal duct and cause profuse salivation as a result of its bitter taste. The duration and frequency of application depend on the severity of ocular inflammation. Very mild inflammation usually is treated only once daily; severe inflammation may require treatment up to three to four times daily to maintain iris dilatation. Because parasympatholytics can cause decreased tear production, they are generally applied until the pupil dilates and then are discontinued until the pupil begins to constrict. The addition of a sympathomimetic agent may help to achieve mydriasis when synechiae have formed already (see Table 3-3).[22]

INFECTIOUS CAUSES OF UVEITIS

Toxoplasma gondii

Diagnosis

Serological evidence of infection by *Toxoplasma gondii* has been reported in as many as 78.5 per cent of cats with anterior and/or posterior uveitis,[4] and ocular lesions of toxoplasmosis have been well-documented.[23,24] No unique ophthalmological findings are associated with *T. gondii* infection. Because cats often become infected by carnivorism, a history of ingesting undercooked meat or hunting activity is common. Acute, polysystemic illness associated with toxoplasmosis is uncommon; fever and hyperesthesia possibly related to muscle inflammation are the most common systemic signs.[23] The actual prevalence of ocular toxoplasmosis is unknown. Many cats with uveitis and positive *T. gondii* serology have no other clinical evidence of disease. When available, ocular histopathology on these cases rarely identifies the organism,[3,25] which makes it difficult to correlate positive serology with ocular infection. This is especially true because many commercial laboratory tests for

T. gondii detect only serum IgG levels. IgG antibodies develop approximately 2 weeks post infection and may remain elevated for years, even in healthy animals.[26] A rising IgG titer (fourfold increase over 2 to 3 weeks) indicates recent or active infection and correlates better with disease. Alternatively, the presence of serum IgM against *T. gondii* can be used as an indication of recent infection, because IgM usually is not detectable 9 weeks post infection.[27]

Detection of *T. gondii* antibody production in the aqueous humor also is used to support the diagnosis of ocular toxoplasmosis in cats.[28,29] This test uses an enzyme-linked immunosorbent assay (ELISA) to detect antibodies to *T. gondii* in both serum and aqueous humor. The Goldman-Witmer coefficient (C-value) is calculated to adjust for antibody leakage from the serum. A C-value greater than 1 indicates that *T. gondii*–specific antibody is being produced in the eye. Because IgM production has only been detected in the aqueous humor of cats with uveitis,[28,29] detection of IgM might indicate disease resulting from the organism. *Toxoplasma gondii* DNA has been amplified from blood and aqueous humor using a PCR assay.[30-32] However, because positive results are found in some apparently healthy research cats, the positive predictive value is not 100 per cent. Although a definitive diagnosis of ocular toxoplasmosis is difficult to make and confirm, treatment with an anti-*Toxoplasma* drug is justified when other causes of uveitis have been ruled out and serological evidence exists of recent or active infection, ocular *T. gondii* antibody production (particularly IgM) is identified, or organismal DNA is found in aqueous humor.

Treatment

Many cats with uveitis are seropositive for *T. gondii* but are otherwise clinically healthy. Most of these cats have anterior uveitis, and topical treatment with 1 per cent atropine (q12h to q24h to effect) and 1 per cent prednisolone acetate or 0.1 per cent dexamethasone is indicated. The frequency of GC treatment varies, depending on the severity of clinical signs, but generally q6h is minimal. If the response is poor, uveitis is severe, or more frequent administration of topical GC is needed but not possible, oral administration of prednisolone usually can be given safely in antiinflammatory dosages without a significant risk of potentiating systemic toxoplasmosis. Once inflammation subsides, the treatment is tapered slowly. If GC are tapered too quickly or discontinued too soon, inflammation will recur. The authors recommend aggressive treatment until uveitis has resolved. Oral GC usually are tapered first, followed by topical.

Systemically ill, *T. gondii*–seropositive cats always should be treated with an anti-*Toxoplasma* drug. In cats with uveitis alone, treatment with an anti-*Toxoplasma* drug can be justified in *T. gondii*–seropositive cats with uveitis, when other causes of uveitis have been ruled out, particularly if GC therapy has not elicited a response. Clindamycin is the drug of choice for treating clinical toxoplasmosis in cats.[27] Although several dose ranges have been reported, the authors currently recommend 10 to 12.5 mg/kg PO q12h for 4 weeks. Liquid clindamycin, administered at 4° C, is tolerated by most cats. Trimethoprim-sulfonamide combination therapy (15 mg/kg PO q12h for 2 to 4 weeks) also can be used for treatment of toxoplasmosis, although it is less suitable because of the potential side effects caused by folic acid deficiency in cats. Frequent monitoring for mental depression, anemia, leukopenia, and thrombocytopenia is required, especially if treatment is longer than 2 weeks.[27] Azithromycin is a potential alternate choice for cats intolerant of clindamycin or sulfa drugs; however, the most appropriate dose for the treatment of toxoplasmosis has not been determined. Nonspecific treatment for uveitis should be used concurrently. To date, no evidence suggests that the use of topical corticosteroids exacerbates systemic toxoplasmosis.

Feline Infectious Peritonitis

Diagnosis

Many cats with FIP are younger than 3 years old[33-35] and most have or will develop other clinical signs of systemic coronavirus disease. Ocular disease accompanied by ascites, thoracic or pericardial effusion, depression, icterus, renal failure, diarrhea, or neurological signs is suggestive of FIP. Ocular lesions are seen most often with the noneffusive or dry form of FIP. Anterior and/or posterior uveitis may be present. Iritis, large keratic precipitates, and clots of fibrin and blood in the anterior chamber are found commonly, along with cuffing of the retinal vasculature and chorioretinitis. Similar to toxoplasmosis, confirming a diagnosis of FIP can be challenging. Studies have shown 25 per cent of household pets and 80 per cent or more of cattery-reared cats carry serum antibodies against feline coronavirus.[31] Current serodiagnostic tests cannot distinguish between antibodies against pathogenic or nonpathogenic coronaviruses.[34-36] Therefore diagnosis usually is based on the combination of clinical signs, physical examination findings, and laboratory evaluation. High serum globulin (>5.1 g/dl), low albumin:globulin ratio, and effusion total protein content greater than 3.5 g/dl also are supportive. Although a high coronavirus antibody titer also is supportive, it does not correlate with disease as well as hyperglobulinemia or low albumin:globulin ratio.[34,37,38] RT-PCR tests on blood are not useful in the diagnosis of FIP because nonpathogenic coronaviruses can be found in the serum or plasma of normal cats.[38,39] Detection of coronavirus RNA in tissues, effusions, or aqueous humor by RT-PCR assay may correlate with the presence of FIP; however, nonpathogenic coronavirus also can be found in the tissues of normal cats.[38]

Treatment

The long-term prognosis for FIP is poor, even with treatment. However, some patients with ocular disease may be managed reasonably for several months to up to a year with medical therapy before the disease generalizes.[40,41] Because the pathogenesis of disease in FIP is immune mediated, the primary goal of treatment is to suppress the immune response. Several protocols have been described, but no current consensus exists regarding optimal treatment for systemic disease.[40,41] For ocular FIP, control of inflammation and prevention of sequelae are the goals of treatment for uveitis caused by FIP; both systemic and topical GC may be required (see Nonspecific Therapy for Uveitis).

Feline Leukemia Virus and Lymphoma

Diagnosis

FeLV-associated diseases are detected most often in young cats. Ocular disease can occur alone or in combination with systemic

signs of illness. Ocular disease does not occur with FeLV infection except by its association with the development of lymphosarcoma (LSA) or by immune suppression and increased susceptibility to other infectious diseases such as *T. gondii* and systemic mycoses. The incidence of ocular disease among clinically affected FeLV-positive cats is reported to be low (2 per cent or less)[42]; however, LSA has been shown to be a common cause of uveitis in enucleated eyes.[25] The ocular lesions of LSA result from neoplastic infiltration of the uveal tract and the clinical signs depend on tumor distribution. Nodular or diffuse infiltration of the anterior and/or posterior uveal tract is possible, and when diffuse, has an appearance similar to uveitis resulting from other causes.[43]

Although isolated ocular LSA probably does not occur, ocular disease may be the primary clinical sign, and many cats with ocular LSA appear to be clinically healthy otherwise.[43] Confirming the diagnosis of ocular LSA requires identification of neoplastic lymphocytes. Sometimes these can be found in aqueous humor cytology, but usually bone marrow cytology or biopsy of tumor located elsewhere in the body is necessary. Testing for infection by FeLV always is indicated because treatment and prognosis may be altered by the FeLV status.[44] However, the usefulness of FeLV testing for diagnostic purposes is limited because most FeLV-positive cats do not have LSA. Conversely, a negative FeLV test does not rule out LSA, because 20 to 70 per cent of cats with confirmed LSA are FeLV-negative.[45] The ELISA for detection of the p27 antigen in the blood is the most widely used, commercially available screening test for FeLV. A PCR assay that can be used to confirm lymphoma has been evaluated for use in dogs; further data are being collected concerning its use in cats.[46]

Treatment

Cats with LSA should be staged and their FeLV status should be determined, because both are related to treatment response and prognosis. Many chemotherapeutic drugs have been used to treat LSA in cats. An excellent review of these drugs and administration protocols can be found in the literature.[47] Ancillary therapy with topical GC and atropine helps control ocular inflammation and prevent sequelae (see Nonspecific Therapy for Uveitis). Systemic GC should be used with caution because their effect on viral replication is not known. Blind, painful eyes may require enucleation. If immunosuppression induced by the virus is considered part of the clinical syndrome, use of immunomodulator therapy or antiviral therapy can be considered. Administration of interferon alpha at 30 U/cat, PO q24h seems to improve quality of life in some cats but does not affect viremia. This protocol has not been assessed in controlled studies of ocular disease associated with FeLV. If antiviral therapy is considered, azidothymidine (AZT) administered as described for FIV may lessen the risk of secondary infections but has not been assessed in controlled studies for treating the ocular manifestations of FeLV.

Feline Immunodeficiency Virus

Diagnosis

Clinical disease in FIV-infected cats usually is detected in older, male cats with a history of exposure to other cats or a history of fighting. Clinical illness often is associated with immunodeficiency and resultant secondary infections, but several primary disease syndromes are attributed to the virus that include uveitis, enteritis, and renal disease. Histopathological evidence of anterior uveitis is found commonly in cats with advanced FIV infection,[48] which confirms the virus as a primary cause of uveitis. Local production of FIV antibodies and antigens in aqueous humor was documented recently in FIV-infected cats with uveitis but not in healthy FIV-seropositive cats.[49] These results support the hypothesis that FIV actively infects the eyes of some cats and can produce uveitis. *Toxoplasma gondii*, *Bartonella henselae*, and *Cryptococcus neoformans* infections all have been detected concurrently in FIV-seropositive cats, which suggests they may be the most common opportunistic infections.[50] Clinically, anterior uveitis, pars planitis, and glaucoma with or without concurrent uveitis have been identified in cats infected with FIV.[51] Pars planitis appears as white, punctate infiltrates concentrated in the peripheral, anterior vitreous.

Presently available commercial PCR tests for FIV are not sufficiently reliable to recommend their use for confirming or ruling out FIV infection. Serum antibodies against FIV can be detected by ELISA, Western blot immunoassay, or immunofluorescent antibody testing. The organism can be detected in blood by PCR or virus isolation. ELISA testing is used most frequently because it is available for in-clinic use.[52] FIV is not cleared by the immune response, and positive antibody tests generally indicate current infection. Because ELISA testing occasionally produces false-positive results, all positive tests should be confirmed with Western blot immunoassay. As an additional confounding factor, antibodies induced by a commercially available FIV vaccine (Fel-O-Vax, Fort Dodge Laboratories) cannot be distinguished from those induced by natural infection on any presently available FIV antibody test, so the vaccination status of all cats with uveitis must be determined. Detection of FIV antibodies does not prove that uveitis is due to FIV. Many FIV-seropositive cats with uveitis have serological evidence of exposure to other pathogens that can cause uveitis.[4,53] Other opportunistic infections should be excluded from the list of differential diagnoses before uveitis is attributed solely to FIV.

Treatment

Treatment of FIV is aimed primarily at management of secondary infections when they are identified. However, ocular inflammation (anterior uveitis and pars planitis) also can be a direct result of the virus. AZT may improve the quality of life and prolong life expectancy in cats with FIV infection.[54,55] When given at 5 mg/kg PO q8-12h, AZT is tolerated by most cats and has minimal toxicity. However, the efficacy of AZT for the treatment of ocular disease induced by FIV currently is unknown. Topical GC and atropine therapy are used to control pain and inflammation as discussed previously. As with FeLV-infected cats, systemic GC should be used with caution because their effect on viral replication is not known.

Systemic Mycosis

Diagnosis

Ocular disease has been reported in cats as the result of disseminated histoplasmosis, blastomycosis, coccidioidomycosis, cryptococcosis, and, rarely, candidiasis.[56,57] Cryptococcosis is the most common of the systemic mycoses seen in cats and

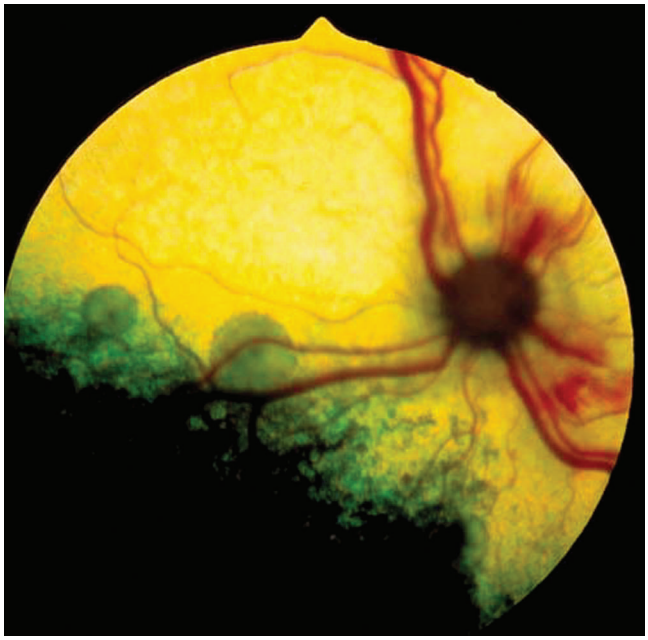

Figure 3-6. Two circular lesions of active inflammation can be seen near the tapetal-nontapetal junction of this eye infected with *Cryptococcus neoformans*. Optic neuritis also is present, indicated by peripapillary edema and hemorrhage.

usually is associated with nasal cavity disease. Cutaneous involvement, especially of the nasal region, and neurological signs also are common.[57,58] Intraocular manifestations of systemic mycoses include chorioretinitis, anterior uveitis, or both, although chorioretinitis alone is most common (Figure 3-6). Definitive diagnosis is made by demonstration of organisms in CSF, vitreous or aqueous humor, or from cytology of nasal exudates, aspirates of lymph nodes, or other tissues. Culture or tissue biopsy and histopathology may be necessary to confirm a diagnosis is some cases. *C. neoformans* antigen testing by latex agglutination and ELISA are available for use with serum, aqueous humor, and vitreous humor, and is superior to antibody testing because positive test results confirm the presence of the organism in the body. Even if the organism is identified by cytology, histology, or culture, serum antigen testing should be performed to serve as a baseline for therapeutic monitoring. Detection of antibodies against *Coccidioides immitis* and *Blastomyces dermatitidis* may be used to aid in the diagnosis if the organisms cannot be found, but false-positive and false-negative results may occur. Serological tests for *Histoplasma capsulatum* are unreliable in cats.

Treatment

Ketoconazole (KTZ), itraconazole (ITZ), and fluconazole (FTZ) are the drugs used most often for treatment of cryptococcal infections in cats. FTZ has the fewest side effects[59,60] and penetrates the CNS better than KTZ or ITZ. FTZ or ITZ are tolerated by most cats at the empirical dose of 50 to 100 mg/cat PO q24h. Treatment with antifungal agents should be continued for at least 1 month after resolution of clinical signs and after the cryptococcal antigen titer has dropped by at least two orders of magnitude.[60,61] When present, anterior uveitis should be treated with a topical GC, such as 1 per cent prednisolone acetate, and atropine. Treatment of chorioretinitis or optic neuritis requires systemic drug therapy. Extremely judicious use of oral GC along with antifungal therapy may be necessary to control the inflammation associated with posterior segment infection.[62] Some eyes with severe posterior segment infection that do not respond to antifungal medication may require enucleation.

Bartonella Species

Diagnosis

B. henselae and *Bartonella clarridgeiae* are two of the causes of cat-scratch disease in human beings.[63] Uveal tract inflammation from *B. henselae* infection in people has been reported.[64] Cats are the apparent reservoir host for *B. henselae* and 55 to 81 per cent of cats are *B. henselae*–seropositive. Fleas transmit the organism, so the incidence of infection is highest in areas with a warm, humid climate that are highly endemic for *Ctenocephalides felis*. The majority of naturally infected or experimentally infected cats show no clinical evidence of disease, but transient fever, lymphadenopathy, stomatitis, and neurological signs have been reported[65] (see Chapter 4). *Bartonella* spp. was suggested as a likely cause of anterior uveitis in one cat based on presence of *Bartonella* spp. antibody production in aqueous humor and a clinical response to doxycycline.[66] *Bartonella* spp. aqueous antibody production was evident in seven of 49 cats with uveitis, but in zero of 49 healthy cats in another study.[67] In that study, three of 24 cats with uveitis and one of 49 healthy cats had *Bartonella* spp. DNA in aqueous humor detected by PCR. These results suggest the organism can invade the eyes of cats and may be associated with uveitis in some cats.

Culture and PCR assay results can be used to confirm *Bartonella* spp. infections in cats.[68] However, because so many healthy cats are seropositive, PCR assay positive, or culture-positive in whole blood, these tests cannot be used to prove ocular bartonellosis. Because *Bartonella* spp. reside within red blood cells and hyphema often accompanies uveitis, detection of the organism in aqueous humor may indicate only bleeding into the eye. Further information concerning the diagnostic utility of aqueous humor testing is needed.

Treatment

Bartonella spp. should be considered on the list of differential diagnoses for cats with uveitis without other known causes, particularly if GC therapy is ineffective and a history of flea infestation exists. If patients fit these criteria, it may be prudent to administer a drug with anti-*Bartonella* activity. Doxycycline was effective given at 5 mg/kg q12h in one cat.[65] However, a dosage of 10 to 22 mg/kg PO q12h for 2 to 4 weeks has been recommended recently, because lower dosages have been shown to be ineffective for eliminating bacteremia.[65] Enrofloxacin at 22.7 mg/cat PO q12h is an alternate protocol for unresponsive cats or cats intolerant of tetracyclines. Lastly, azithromycin at 10 mg/kg PO q24h may be effective but has not been studied for the treatment of *Bartonella*-associated ocular disease in cats. Topical, nonspecific therapy should be used concurrently to treat uveitis.

Feline Tuberculosis

Diagnosis

Feline tuberculosis (TB) is caused most commonly by ingestion of uncooked meat or unpasteurized milk from cattle infected with *Mycobacterium bovis*. Because of eradication measures, the prevalence of bovine TB, and thus feline TB, is rare in the United States.[69] Chronic anterior uveitis, granulomatous chorioretinitis, ocular hemorrhage, and retinal detachment may be found in cases of feline tuberculosis.[69] Other clinical signs reflect the site of primary infection, and often are gastrointestinal. Diagnosis is made by identification of acid-fast bacilli from tissue aspirates or biopsy specimens. Intradermal skin testing and serological testing are unreliable in cats. Commercially available PCR tests likely will be available in the near future.[70]

Treatment

Although cats with *M. bovis* infection have been treated successfully with oral rifampin (4 mg/kg/day for 2 to 5 months) after excision of skin lesions, whether to treat is a serious concern because of the human health hazards and the potential for development of drug resistance.[70]

Intraocular Parasite Migration

Intraocular parasite migration (ophthalmomyiasis) is an uncommon cause of ocular disease in cats. Most cases are caused by larval stages of the rabbit and rodent bot fly, *Cuterebra* spp.,[71,72] although intraocular migration of an adult nematode also has been reported.[71] Anterior chamber involvement can cause acute, severe anterior segment inflammation, which often is poorly responsive to medical therapy. Retinal degeneration (by an unknown mechanism) may be a sequela to anterior segment *Cuterebra* spp. migration.[73,74] Posterior segment parasite migration causes minimal inflammation when confined to the subretinal space. Diagnosis is made by observing the parasite itself, or by observing the typical, curvilinear subretinal migration tracts.[74]

Treatment

When possible, the parasite should be removed surgically, followed by aggressive medical management of uveitis.

Feline Herpesvirus 1

Herpesvirus infections of people have been associated commonly with uveitis.[75] Until recently, feline herpesvirus-1 was believed to cause only conjunctivitis and keratitis. Serum and aqueous humor were collected from healthy cats, cats with idiopathic uveitis, and cats with suspected *Toxoplasma* spp. uveitis.[76] FHV-1 antibodies were measured in serum and aqueous humor, and FHV-1 DNA was measured in aqueous humor by PCR assay. Local production of FHV-1 antibodies was detected frequently in cats with uveitis; C values greater than 8 were detected only in cats with idiopathic uveitis. Additionally, herpesvirus DNA was detected in aqueous humor in 11 of 73 cats with uveitis but in only one of 22 healthy cats. These results show that FHV-1 enters the eyes of cats and may be associated with uveitis. Because the majority of client-owned cats are vaccinated or preexposed to FHV-1, antibodies are detected in most of their sera.[77] Thus serum antibody detection has no benefit in the diagnosis of FHV-1-associated uveitis. Further data are needed before treatment recommendations can be made.

Ehrlichia Species

Ehrlichia spp. are gram-negative rickettsia that infect a wide variety of hosts and usually are tick-borne. *Ehrlichia* spp. infections have been detected in some dogs with uveal tract inflammation.[78] The world's literature contains reports of a small number of cats with ehrlichiosis. The clinical syndromes reported have not included uveitis, but otherwise are very similar to those in dogs.[78,79] In an epidemiological study that compares incidence of clinical signs in cats with and without *Ehrlichia* spp. serum antibodies, a statistical association was made with ocular discharge and uveitis.[79] Further work is required to elucidate the involvement that *Ehrlichia* spp. infection has in cats with uveitis.

COMPLICATIONS OF UVEITIS

Aggressive treatment of uveitis is necessary to avoid secondary sight-threatening complications. Formation of synechiae can lead to glaucoma by obstructing the flow of aqueous humor through the pupil and/or out the iridocorneal angle. The intraocular pressure (IOP) of an eye with glaucoma secondary to anterior uveitis may be in the normal range because of the simultaneous decrease in aqueous humor production and outflow. Measurement of IOP should be performed on all patients with anterior uveitis. The development of secondary glaucoma should be suspected when IOP is greater than 10 mm Hg in an eye with anterior uveitis, and the eye should be monitored closely for increasing IOP. Glaucoma is treated best with carbonic anhydrase inhibitors and beta-blockers to decrease aqueous humor production. Carbonic anhydrase inhibitors can be administered orally (dichlorphenamide 0.5 to 1.5 mg/kg q12h to q8h or methazolamide 3 to 4 mg/kg q12h) or topically (dorzolamide or brinzolamide q8h). Systemic side effects (vomiting, diarrhea, panting, depression, potassium depletion) are less likely with topical treatment. Timolol, betaxolol, carteolol, levobunolol, and metipranolol are topical beta-adrenergic blocking agents and are administered q12h. Beta-blockers should be used with caution in animals showing signs of heart failure or bronchial asthma because of potential systemic absorption.

A cataract may result from uveitis, especially when chronic. The extent of cataract formation is dependent on the severity and duration of inflammation and may involve only the lens capsule or may affect the entire lens. Lens subluxation or complete luxation also can occur as a result of chronic uveitis and is especially common when the eye has become buphthalmic as the result of glaucoma. Removal of a cataract or a luxated lens caused by chronic or recurrent anterior uveitis usually is not rewarding, because uveitis remains a problem and may be exacerbated by surgery.

Chorioretinitis can lead to partial or complete retinal detachment. The end result of chorioretinitis is degeneration of the affected retina. Irregularly shaped areas of tapetal hyperreflectivity most often are indicative of retinal degeneration secondary to previous inflammation. Extensive chorioretinitis

results in visual impairment or, if the entire retina is involved, complete blindness resulting from retinal degeneration.

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Chapter 4

Bartonellosis

Barrak Pressler

Although more than 100 years old, Robert Koch's postulates still are used as standards for establishing that a given microorganism is an agent of disease.[1] However, we now know that because of the complex interaction of genetics, microbes, and the host's immune system, disease development is not always as simple as Koch believed. The postulates are easy to fulfill for an organism that is nearly universally pathogenic. But what of a microbe that causes disease only in an individual with a particular genetic make-up, who must have been exposed previously to a second microorganism, and only when the host is exposed to the microbe at a time of mucosal injury? In such a scenario the pathogen may never even be suspected if in the absence of the other precipitating factors it is part of the normal host flora. Many conditions we consider to be "idiopathic" or "immune-mediated" may truly have an infectious etiology but require more than Koch's postulates to identify the causative organisms.

Feline bartonellosis is the prototypical example of this challenge in infectious disease research. Cats rarely develop the same *Bartonella* spp.–induced disease syndromes as other species, but what particular feline or microbial factors are protective? The majority of naturally infected cats appear to be asymptomatic reservoirs, so why do experimentally infected cats exhibit clinical abnormalities more commonly? After 15 years of research, we are still not even sure what cells *Bartonella* spp. infect in cats. Given these gaps in our knowledge, it is unlikely that Koch's postulates will be fulfilled for *Bartonella* spp.–induced disease in the near future. However, our knowledge of this genus is increasing rapidly, which facilitates educated approaches to diagnosis and treatment of infected animals.

ETIOLOGY

Bartonella spp. are facultatively intracellular, gram-negative bacilli that infect a variety of animals.[2] *Bartonella* spp. are within the alpha-2 Proteobacteria; closely related bacteria of veterinary importance are *Brucella* spp. and the Rickettsiae. The genus *Bartonella* has undergone major reorganization as molecular techniques have defined genetic relationships between known species and improved the detection of new species. The previously separate genera *Rochalimaea* and *Grahamella* were merged into *Bartonella* in the early 1990s.[2,3] Approximately 20 species of *Bartonella* are recognized currently; however, new species have been defined as recently as 2002, and further changes in the classification of *Bartonella* undoubtedly will occur in the coming years.[2,4]

Most *Bartonella* spp. have animal reservoir hosts, but only a minority of these infect dogs and cats (Table 4-1).[4] The four species that have been isolated from cats are *B. henselae*, *B. clarridgeiae*, *B. koehlerae*, and *B. bovis* (*weissii*). *B. henselae* is classified further into two genotypes, *B. henselae* I and *B. henselae* II, previously known as *B. henselae* Houston I strain and *B. henselae* Marseilles strain, respectively.[5] These genotypes are differentiated by the 16S ribosomal RNA gene sequences.[5] Differences in other proteins also have been demonstrated, and these are likely responsible for the variation in antibody responses in infected cats.[5,6] Coinfection with both genotypes of *B. henselae* can occur in cats, as can coinfection with either *B. henselae* genotype and *B. clarridgeiae*.[7-12]

EPIDEMIOLOGY

The domestic cat is the reservoir host for *B. henselae*, and *B. henselae* is the *Bartonella* spp. isolated most commonly from cats.[2] The natural history of *B. henselae* infection has been deduced largely from experimental studies, because naturally infected cats usually are asymptomatic and thus not identified routinely in clinical practice. Although *B. henselae* is adapted for infection of cats, its larger genome and numerous potential vectors indicate it is less specialized than other members of the genus.[13,14] In addition to the domestic cat, wild felids also can be infected, but the clinical implications in these species are still unknown.[15,16]

The prevalence of *B. henselae* and *B. clarridgeiae* in cats has been studied throughout the world (Figure 4-1). Infected or exposed cats have been reported on all continents except Antarctica and South America. The lack of *Bartonella* spp.–infected cats from South America doubtlessly results from inadequate prevalence studies rather than absence of infected cats, particularly because *B. henselae*–induced disease has been reported in South American people. Unfortunately the

Table 4-1 | **Clinical Signs or Disease Syndromes Caused by *Bartonella* Species Infection in Dogs and Cats***

BARTONELLA SPP.	CLINICAL SIGNS OR DISEASE SYNDROMES
B. bovis	Asymptomatic bacteremia (C)
B. clarridgeiae	Asymptomatic bacteremia (C); endocarditis (D); lymphocytic hepatitis (D)
B. elizabethae	Anemia (D)
B. henselae	Asymptomatic bacteremia (C,D); endocarditis (C); granulomatous hepatitis (D); lymphadenitis/lymphadenopathy (C,D); neurological disease (D); ocular disease (chorioretinitis, uveitis, etc.) (C,D); peliosis hepatitis (D); stomatitis/gingivitis (C); thrombocytopenia (D); urinary tract disease (C)
B. koehlerae	Asymptomatic bacteremia (C)
B. quintana	None†
B. vinsonii subsp. *berkhoffi*	Asymptomatic bacteremia (D); cardiac disease (arrhythmias, endocarditis, myocarditis) (D); granulomatous lymphadenitis (D); granulomatous rhinitis (D); uveitis/choroiditis (D)
B. washoensis	Endocarditis (D)

C, Cats; *D*, dogs.
*Only clinical signs/disease syndromes from animals with natural infection listed. Data compiled from references 26,35,44,66-71,75-77,83-86.
†Seroreactivity reported in cats, but no confirmed cases of infection (see text).

comparison of prevalence studies between countries is difficult because each report uses different techniques for diagnosing infection or seropositivity. Regardless, significant regional differences exist in the overall prevalence of *Bartonella* spp. in addition to the relative prevalence of the different *Bartonella* spp. within populations of cats.

Regional prevalence throughout the world of both *Bartonella* spp. exposure and bacteremia increases as yearly average temperature and precipitation increase.[10,17] This combination of climatic variables is the most suitable for fleas, the insect vector for *B. henselae* and presumptively *B. clarridgeiae*.[18,19] Regions unsuitable for fleas (as a result of severe winters, such as in Norway and Alaska, or low precipitation, such as the southwestern United States) have a low prevalence of *Bartonella* spp.–positive cats.[17,20] Conversely, regions with mild year-round weather (such as the southeastern United States, California, central Europe, the Middle East, southern Africa, and the Philippines) have a higher number of exposed and infected cats.[9,17,21-25]

For unknown reasons, large regional variations exist between the relative prevalence of *B. henselae* genotype I versus genotype II, and *B. henselae* versus *B. clarridgeiae*. For example, less than 10 per cent of *B. henselae* cases in Japan are genotype I, whereas most cases of *B. henselae* are genotype II in the Philippines.[9,10] *B. henselae* genotype II predominates in northern and central Europe, but western Europe has an approximately equal number of both genotypes.[7,12,26-29] Regional differences within the United States also exist for *B. henselae* genotype distribution.[25] As with *B. henselae*, the seroprevalence and infection rate for *B. clarridgeiae* vary throughout the world.*

Many studies have identified factors associated with *B. henselae* infection in cats. Some results are conflicting; however, most support an increased risk of bacteremia in feral cats, shelter cats, young cats, cats with partial or complete outdoor lifestyles, cats with fleas, and cats in multicat environments.† Cat gender, retroviral infection, *Toxoplasma gondii* serostatus, and illness in general are not associated with bacteremia or exposure.‡ Risk factors for seropositivity are the same as for bacteremia, except that prevalence of seropositivity increases with cat age as the prevalence of bacteremia decreases.[25,33,38,39] Other factors that have been studied less often but appear to have no association with infection or exposure include visits to veterinarians, declawing, presence of dogs in the same household, and attendance at cat shows.[33,34] Factors that have been reported once as possibly significant but have not been confirmed in other reports include presence of antibodies against coronavirus, spumavirus, or *Borrelia burgdorferi*.[26,39]

Less is known of the natural epidemiology of the non–*B. henselae Bartonella* species that infect cats. As with *B. henselae*, cats are the only identified reservoir of *B. clarridgeiae*; however, rate of exposure to and infection with *B. clarridgeiae* usually is much lower than for *B. henselae*.§ Because fleas from cats have been found to carry *B. clarridgeiae,* the route of infection in cats is presumed to be similar to *B. henselae*.[19,40] Identified risk factors for *B. clarridgeiae* exposure and infection are similar to those of *B. henselae*.

Natural infection with *B. koehlerae* has been reported in three cats (two in California and one in France).[41,42] Because cats infected experimentally with *B. koehlerae* fail to demonstrate the same relapsing bacteremia as cats infected with other *Bartonella* spp., the prevalence of infection likely is underestimated by these rare reports.[43] *B. bovis* (originally reported as *B. weissii*) has been cultured from only four cats, all in the United States.[44] Cats reported with *B. koehlerae* or *B. bovis* infection did not have obvious environmental or historical findings different from other *Bartonella* spp.–infected cats.[41,42,44]

Although seropositivity to *B. elizabethae* and *B. quintana* has been reported in cats, infection has not been demonstrated.[21,24,38] Whether these results represent true exposure or cross-reactivity between *Bartonella* spp. is unclear. *B. henselae* antibodies are known to cross-react with *B. quintana*; however, *B. quintana* has been isolated from cat fleas.[19,21] Regardless of whether exposure to these *Bartonella* spp. indeed occurs, they are of unknown clinical significance in cats.

PATHOGENESIS AND IMMUNOLOGY

Although not proven definitively, current thought assumes that after inoculation *B. henselae* and *B. clarridgeiae* enter the bloodstream, infect erythrocytes, and cause bacteremia. Initial bacteremia in experimental cats lasts from 2 to 32 weeks, beginning 1 to 2 weeks after inoculation.[45-53] *Bartonella* spp. DNA often can be amplified from cat blood for several weeks after blood cultures become negative.[52] Recurrent episodes of

*References 7,9-11,25,27-32.
†References 7,9,10,12,24,25,31,33,34.
‡References 12,25-27,31,33-37.
§References 7,9-11,25,27-32.

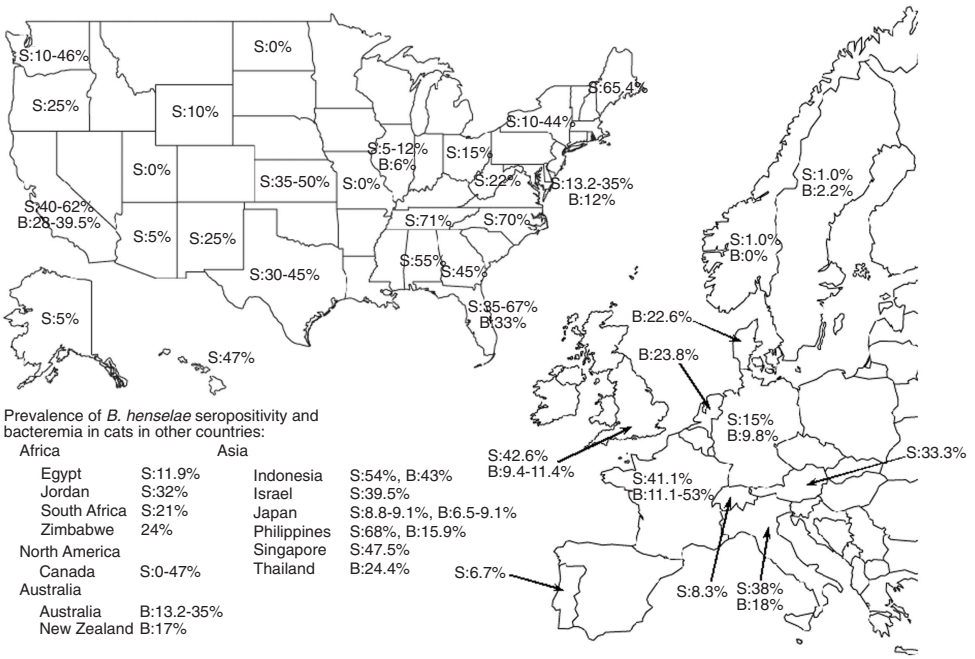

Figure 4-1. Prevalence of *B. henselae* seropositivity and bacteremia in cats throughout the world. *S,* Prevalence of seropositive cats; *B,* prevalence of bacteremic cats. Data compiled from references 7,9-12,17,20-33,36-39,61,87-95. (Map courtesy of WorldAtlas.com www.worldatlas.com.)

bacteremia follow at unpredictable intervals, with the frequency of bacteremia decreasing with age.[48,52-54] The site of persistent *Bartonella* spp. infection during periods of abacteremia is still unknown. However, suspected sites include vascular endothelial cells, erythrocytes, lymph nodes, and cells of the central nervous system.[55-60] No definitive proof exists that cats ever become free of infection.

Humoral Immunity

The antibody response to acute experimental *B. henselae* or *B. clarridgeiae* infection is similar to other diseases. Anti–*Bartonella* spp. IgM is first detected within 1 week of inoculation followed by a rise in IgG 1 to 2 weeks later.[47,50,51] The IgG titer peaks after 5 to 10 weeks and remains persistently elevated for months to years.[18,47-51,53,54] Rare naturally infected bacteremic but seronegative cats have been identified.[7,25,31,61] These cats may have had positive titers that declined to extremely low concentrations over time, or a subset of infected cats may never seroconvert. Although some studies suggest that antibody titer may correlate with bacteremia, this association is too unreliable to be clinically useful.[33,54]

After experimental infection with one genotype or species of *Bartonella,* subsequent challenge with the identical genotype or species results in a protective rise in anti–*Bartonella* spp. IgG, preventing illness or bacteremia.[62,63] However, challenge with a different genotype or species does not result in cross-protection, and bacteremia with the second *Bartonella* spp. occurs.[62,63] The exception to this is in cats first infected with *B. henselae* genotype I and then challenged with *B. henselae* genotype II; these cats appear immune to both genotypes, although the reverse order of infection does not confer the same immunity.[63] Natural infection with multiple genotypes and species of *Bartonella* has been reported several times.[7-12]

Anti-*Bartonella* spp. antibodies develop against many bacterial proteins.[5,64] Considerable overlap exists in antibody targets between species, and thus cross-reactivity between the antibodies against different *Bartonella* spp. occurs.[21,40,43] Antibodies against the different proteins develop over a period of several weeks.[64]

Cell-Mediated Immunity

Cell-mediated immunity against *Bartonella* spp. has not been studied extensively. Peripheral blood CD4:CD8 lymphocyte ratio remains within reference range during acute infection despite marked hyperplasia of lymphoid organs.[47,53] *B. henselae*–specific lymphocytes that proliferate in response to *B. henselae*–derived proteins are detectable within spleens from experimentally infected cats.[47,49] Delayed-type hypersensitivity in *B. henselae*–infected kittens causes mild local reactions after intradermal inoculation of bacterial lysates.[49]

TRANSMISSION

The vector for *B. henselae* is the cat flea.[18] Transmission is thought to occur by intradermal inoculation of infected flea feces or regurgitation of flea saliva into the bite wound during feeding.[18,65] Ingestion of infected fleas or their feces does not result in infection.[65] Experimentally infected flea-free cats do not transmit *B. henselae* to co-housed cats despite fighting and playing behavior that includes traumatic injuries.[18,53] *B. henselae* is not transmitted transplacentally or transmammary to kittens from bacteremic queens.[43,49,53] Kittens born to infected mothers acquire maternal anti–*Bartonella* spp. antibodies from colostrum that is first detectable at 2 weeks of age and then wanes to undetectable concentrations by 10 weeks.[49,53] Males do not acquire *B. henselae* after mating with infected

females.[49,53] Urine from *Bartonella* spp.–infected cats does not transfer disease when used to inoculate naïve cats intradermally.[48] Transmission of other *Bartonella* spp. has not been studied in cats; however, cat fleas are known to carry *B. clarridgeiae* and *B. koehlerae* and thus also may serve as vectors for these species.[19]

CLINICAL SIGNS

Complete absence of clinical signs is typical of most cats with *Bartonella* spp. infection. Most epidemiological studies have failed to show a statistical association between illness in cats and *B. henselae* or *B. clarridgeiae* bacteremia or seropositivity. However, because (1) a few studies have linked bartonellosis to particular clinical signs in cats, (2) reports of *Bartonella* spp.–induced disease in all species are increasing, (3) experimental infections occasionally result in clinical signs in cats, and (4) some ill cats respond to appropriate antibiotic therapy, bartonellosis remains a differential diagnosis for certain clinical signs and syndromes in cats.

Naturally Infected Cats

Illness in general (defined as a cat brought to a veterinarian for any reason other than preventive care) is not associated with bartonellosis.[12,25,26,34] However, when specific disease syndromes are compared between *Bartonella* spp.–positive and *Bartonella* spp.–negative cats, stomatitis twice has been associated with *B. henselae*.[26,35] Anecdotally, some cats with intractable oral disease respond to appropriate anti–*Bartonella* spp. treatment. Other conditions that may be more prevalent in *Bartonella* spp.–infected cats are lymphadenopathy and renal or urological disease.[26,35]

Bartonella spp. are the most common cause of culture-negative endocarditis in dogs and human beings.[66] Patients present typically with the same history, physical examination, and cardiac-related abnormalities as with non–*Bartonella* spp. endocarditis; however, no bacteria are isolated by routine aerobic blood cultures.[62] One case of *B. henselae* endocarditis has been reported in a cat.[67] Although *Bartonella* spp.–specific blood cultures were negative, light microscopic examination of the aortic valve revealed intraendothelial organisms consistent with a *Bartonella* spp., and *B. henselae* DNA was amplified from valve tissue.[67]

Several reports have identified *Bartonella* spp. as a possible cause of uveitis in cats[68-70] (see Chapter 3). *Bartonella* spp. infection is a well-recognized cause of uveitis in people and was suspected to be a cause of anterior uveitis and choroiditis in one dog.[4,71] Cats with inflammatory ocular disease have a high prevalence of anti–*Bartonella* spp. antibodies; however, seropositivity was not statistically significant in the one study that compared cats with uveitis to a control population.[68,70] The aqueous humor versus serum anti–*Bartonella* spp. antibody titer ratio may be used as an aid in the diagnosis of *Bartonella* spp.–induced uveitis; local antibody production in the eye supports the diagnosis of ocular bartonellosis.[69,70] As with serum anti–*Bartonella* spp. antibodies, the prevalence of *B. henselae* DNA within aqueous humor of cats with uveitis is not significantly different from seropositive healthy cats. However, antibodies may decrease the number of viable organisms below the level of detection by PCR, or inflammation may be a chronic process that progresses despite the clearance of infection.[70]

Experimentally Infected Cats

Most experimentally infected cats have no apparent clinical signs during the chronic, relapsing bacteremia stage of *Bartonella* spp. infection. However, a transient febrile illness can occur immediately after inoculation of specific pathogen-free cats.[47,48,50,51] Between 1 and 3 days after intradermal inoculation, cats develop a localized inflammatory lesion that progresses and resolves spontaneously over 2 weeks.[50,51] The inoculation site typically is erythematous and firm, and pustules may form.[50,51] Approximately 1 week after infection, kittens become lethargic and anorexic with fever, pale mucous membranes, peripheral lymphadenopathy, and a stiff gait.[47,48,50,51] Lymph node and splenic enlargement develop secondary to marked lymphoid hyperplasia.[47,50] The time between inoculation and development of clinical signs is proportional to the number of bacteria used in the inoculum; smaller doses result in slower development of illness.[47]

Recovery from the initial transient illness corresponds to resolution of the first bacteremic episode.[47,48,51] In all cats, lymphadenopathy regresses, skin lesions heal, and fever resolves without incidence.[47,51] Later episodes of bacteremia do not cause recurrence of clinical signs, and no correlation exists between bacteremia and antibody titer.[54] Clinicopathological abnormalities during acute and chronic infection are rare, although eosinophilia has been reported.[48,50,54,72]

Several additional abnormalities have been reported more rarely in experimental cats. Behavioral changes and signs of central neurological disease including star-gazing, obtundation, and postural deficits with decreased conscious proprioception may occur in cats infected as kittens.[48,51] These episodes last from 1 to 4 days, occur 1 week to 4 months after inoculation, and coincide with periods of bacteremia.[48,51] Nystagmus and whole-body tremors developed in two queens infected as adults.[73] Cataracts or vitreal degeneration developed in several cats infected as kittens.[48,70] Finally, *B. henselae* infection may prevent conception or cause fetal resorption in infected queens.[73]

Some reports suggest that clinical signs in experimentally infected cats may be related to the species or strain of *Bartonella* used.[31] Although the presence and severity of complications in people with cat scratch disease may be associated with *B. henselae* genotype, studies of naturally infected cats do not support this difference in pathogenicity.[52,54,63,74]

Other Species

Unlike in cats, *Bartonella* spp. are considered pathogens in human beings and dogs. Familiarity with the disease syndromes and clinical signs associated with bartonellosis in these species may allow recognition of unusual *Bartonella* spp.–induced diseases in cats. Endocarditis and uveitis are discussed earlier in this chapter. Cat scratch disease, proliferative vascular diseases, Oroya fever, and trench fever are diseases induced by *Bartonella* spp. in people that may have analogous conditions in animals. Several other clinical signs and diseases have been associated with *Bartonella* spp. infection in dogs, although definitive proof of causation is lacking (see Table 4-1).

Cat scratch disease is a chronic, localized, suppurative lymphadenitis in people that usually follows traumatic injury by a cat.[4] Lymphadenopathy lasts several months, is nonpainful, and usually is not accompanied by systemic signs of illness.[4]

Table 4-2 | **Advantages and Disadvantages of Available *Bartonella* Species Diagnostic Tests**

TEST	ADVANTAGES	DISADVANTAGES
Immunofluorescent antibody test (IFA)	High negative predictive value (cats with negative titers are very unlikely to be infected) Offered by many commercial laboratories Antibody tests much more rapid than other tests	Low positive predictive value (cats with positive titers may or may not be infected; some cross-reactivity with other bacteria occurs) Unable to differentiate between *Bartonella* species
Western blot antibody test	Widely available Antibody tests much more rapid than other tests	No published studies evaluating accuracy, sensitivity, or specificity Unable to differentiate between *Bartonella* spp.
Blood culture	Gold standard for diagnosing *Bartonella* spp. infection in cats High positive predictive value (cats with positive culture are definitely infected) High specificity	Results may require 2-8 weeks Low negative predictive value (cats with negative cultures may be infected but not bacteremic) Unable to differentiate between *Bartonella* species Samples require special handling and culture conditions Not widely available
PCR	Likely has high positive predictive value and specificity Able to differentiate between *Bartonella* spp. Best diagnostic test for tissue samples other than blood	Few published studies evaluating accuracy, sensitivity, or specificity Very limited availability

However, some patients develop systemic complications, including fever, myalgia/arthralgia, splenomegaly, and central nervous system or ocular disease.[4] Although the typical lymphadenitis of cat scratch disease has not been reported in animals, granulomatous lymphadenopathy in dogs and transient lymphadenopathy after acute infection in cats do occur.[47,50,75] As reviewed previously, some of these complications occur in acute (fever, arthralgia/myalgia, splenomegaly) or chronic (CNS or ocular disease) *B. henselae* infections in cats.*

Bacillary angiomatosis, peliosis hepatis, and verruga peruana are angioproliferative lesions that affect various organs in people.[4] Several *Bartonella* spp. have been implicated, including *B. henselae*, *B. quintana*, and *B. bacilliformis*.[4] Peliosis hepatis associated with *B. henselae* has been reported in a dog.[76] No reports of angioproliferative diseases exist in cats. The pathogenesis of these vascular lesions is unknown, but is related presumptively to the presence of intraendothelial organisms.[4,57]

Oroya fever is an acute febrile disease in human beings caused by *B. bacilliformis*.[4] Severe intravascular hemolysis secondary to erythrocyte invasion by organisms occurs; mortality is high in untreated patients.[4] No analogous disease has been reported in animals, although anemia has been associated with *B. elizabethae* infection in a dog.[77] Trench fever was described initially as an acute, transient febrile illness caused by *B. quintana* in people.[4] It is now diagnosed more commonly as a cause of chronic asymptomatic bacteremia, analogous to natural bartonellosis in cats.[4]

DIFFERENTIAL DIAGNOSIS

Given the diverse manifestations of *Bartonella* spp. infections, the differential diagnoses for infection in cats are extensive. The transient fever and lymphadenopathy seen in acute infection should be differentiated from acute viral infections (particularly FeLV and feline immunodeficiency virus [FIV]), bacterial sepsis, toxoplasmosis, and systemic fungal diseases. Noninfectious diseases, particularly lymphoma, also should be considered in any cat with these vague signs of illness.

More specific syndromes ascribed to *Bartonella* spp. infection in cats have differential diagnoses that are reviewed thoroughly elsewhere. In general, causes of uveitis in cats include viral, protozoal, fungal, and neoplastic diseases. The more ubiquitous bacteria, particularly the enteric bacteria, should be considered in cats with endocarditis. Calicivirus (see Chapter 1), feline odontoclastic resorptive lesions (see Chapter 9), and hypersensitivity reactions are common causes of oral inflammation or stomatitis that should be excluded before consideration of bartonellosis.

DIAGNOSIS

In cats, asymptomatic *Bartonella* spp. infection must be differentiated from *Bartonella* spp.–induced disease. The former is relatively straightforward to diagnose: positive blood culture or successful amplification of *Bartonella* spp. DNA by PCR is diagnostic for infection. However, no single diagnostic test can be used to diagnose clinical bartonellosis in cats. Clinicians must always keep in mind that disease in cats secondary to *Bartonella* spp. infection is rare. Because cats are natural reservoirs for *B. henselae* and *B. clarridgeiae,* exclusion of differential diagnoses and response to therapy are just as important for diagnosing clinical bartonellosis as is demonstration of seroreactivity or documenting presence of organisms. Several diagnostic tests are commercially available, and others are offered at research or specialty laboratories (Table 4-2).

Antibody Testing

The most widely available tests for *Bartonella* spp. detect the presence of anti–*Bartonella* spp. antibodies. These tests include the immunofluorescent antibody test (IFA), which detects the presence of antibodies against whole organisms, and the Western blot, which detects antibodies against proteins from bacterial lysates. Most published studies on *Bartonella* spp. infection and seroprevalence have used the IFA test, and the

*References 47,48,50,51,68-70,73.

positive and negative predictive values of this test have been determined.[7,25,31,33] Studies examining the accuracy of the Western blot are not available. The commercially available IFA and Western blot tests have not been compared directly to one another.

The high prevalence of seroreactivity to *B. henselae* and *B. clarridgeiae* makes antibody testing a poor method for diagnosing *Bartonella* spp.–induced disease. As with any serological test, the presence of antibodies merely means that a patient has been exposed to the organism. In general, the long lifespan of plasma cells and long half-life of IgG ensure that antibodies persist in circulation long after organisms have been cleared. For cats in particular, a poor correlation exists between the presence of anti–*Bartonella* spp. antibodies and illness.[7,25,31,33] Other limitations to the antibody tests include inability to discriminate between different *Bartonella* spp. because of antibody cross-reactivity, and lack of correlation between titer magnitude and bacteremia, time since infection, or presence of clinical signs.*

Antibody testing in cats may be useful in two situations. First, the high negative predictive value (>90 per cent) of the IFA test allows rapid screening of cats.[25,31] Although positive results do not always imply infection, absence of anti–*Bartonella* spp. antibodies is likely to mean that a patient is not infected. However, because a small number of infected cats remain seronegative, this screening method does not identify all infected cats reliably.[7,25,31,61] Second, a fourfold or greater increase in antibody titer may imply recent infection. This likewise should be interpreted with caution, because naturally and experimentally infected cats may have titers that fluctuate widely over time.[54] A large increase in antibody titer should be accompanied by clinical signs to be supportive of *Bartonella* spp.–induced disease.

Blood Culture and PCR Testing

Definitive diagnosis of *Bartonella* spp. infection requires isolation by blood culture or DNA amplification by PCR. Collection of blood for either of these tests is best done before initiation of antibiotic therapy. Laboratories should be notified that *Bartonella* spp. are suspected when submitting blood for culture because samples require special processing and a variety of culture media should be used.[25,27] Most *Bartonella* spp. cultures are positive within 2 weeks of plating, although some isolates may take up to 2 months to grow.[78] Alternatively, PCR of blood may offer a more rapid method of diagnosing *Bartonella* spp. infection than culture. Theoretically the sensitivity of PCR is equal to or greater than that of culture; however, this test may vary between laboratories and few studies have been published using this diagnostic test.[54] As with antibody testing, clinicians should not assume that positive culture or PCR results mean that a cat's clinical signs are due to *Bartonella* spp. infection. The majority of culture- and PCR-positive cats are asymptomatic.

Testing Considerations

The previous discussion implies the diagnosis of *Bartonella* spp.–induced disease in cats may be impossible. However, despite the less-than-perfect tests available, a practical approach to diagnosis can be used. Because *Bartonella* spp. infection in cats is asymptomatic in the vast majority of cases clinical bartonellosis should be considered a "rule-out" diagnosis. Testing should be considered only after more likely differential diagnoses have been excluded in patients that have clinical signs potentially associated with *Bartonella* spp.

Cats with clinical syndromes that have a strong association with *Bartonella* spp. infection (such as endocarditis) should be tested earlier in the diagnostic work-up. In cats, this includes endocarditis and possibly uveitis. Patients with clinical signs rarely attributed to bartonellosis (such as lymphoplasmacytic stomatitis, anemia, or fever) also may be tested for *Bartonella* spp., although testing in these cases likely should occur later in the diagnostic plan. Once the decision has been made to test for *Bartonella* spp., antibody testing can be an appropriate initial screen. Paired titers may be considered in acutely ill cats; single resting titers are sufficient in patients with chronic illnesses. Negative titers can be considered adequate for excluding bartonellosis in chronically ill cats, whereas positive titers can be followed by blood culture, PCR, or antibiotic trials as appropriate. Culture of blood is recommended in all cases of endocarditis because this disease is always presumed to be secondary to bacteremia. Serial antibody titers likely are not useful for monitoring response to treatment, although some laboratories do claim to see a decrease in titer after antibiotic therapy. Repeat culture or PCR can be performed if desired, but because of the relapsing nature of *Bartonella* spp. bacteremia, negative results may be transient.

TREATMENT

In vitro susceptibility testing of *Bartonella* species thus far has failed to predict susceptibility in vivo.[4] *Bartonella* spp. tested on standard culture media are susceptible to most antibiotics; however, these results do not take into account the intraerythrocytic location of *Bartonella* spp. organisms in infected animals. Susceptibility testing of *Bartonella* spp. cocultivated with whole cells has shown that most antibiotics are only bacteriostatic, although aminoglycosides hold the most promise for killing intracellular organisms.[4,72]

Trials in naturally and experimentally infected cats are few. A definitive treatment has not been established at this time, and published studies contradict one another. Enrofloxacin and doxycycline have been reported to reduce or eliminate circulating *B. henselae* in naturally infected cats when administered at standard doses for 2 to 4 weeks.[72] However, most cats that did not have organisms isolated by blood culture during or soon after treatment were bacteremic again weeks to months after cessation of therapy.[72] In experimentally infected cats, one study reported no benefit from treatment of *B. henselae*–infected cats with amoxicillin or enrofloxacin; however, erythromycin or tetracycline depressed the number of circulating organisms without decreasing the length of bacteremia.[46] Another study showed reduction or clearance of *B. henselae* with doxycycline or amoxicillin with or without clavulanic acid, whereas enrofloxacin treatment was ineffective in all cases.[45]

Although not evaluated in any controlled study, the current recommended drug for treatment of *Bartonella* spp.–induced disease in cats is azithromycin. The regimen used is usually 5 to 10 mg/kg PO q24h for 5 days, then q48h for 40 days. No

*References 12,18,26,34,47-51,53,54,72.

studies have been reported on the efficacy of this drug in cats for treatment of any disease, and this dosage is based solely on pharmacological data, human literature, and anecdotal reports.

As with cats, optimal treatment of bartonellosis of human beings has not been studied systematically. In the only randomized prospective double-blind study in people with cat scratch disease resulting from *B. henselae,* azithromycin was shown to decrease lymph node size by 80 per cent in half of all treated patients, versus 7 per cent of placebo-treated controls.[4] However, no beneficial effect was observed for prevention of complications such as endocarditis. Doxycycline and rifampin combination therapy is the treatment of choice in patients with complicated cat scratch disease infections.[4] Vascular proliferative diseases in people caused by *Bartonella* spp. are treated with erythromycin or doxycycline.[4] Studies on *Bartonella* spp. endocarditis support the use of gentamicin with doxycycline, with rifampin to be substituted if renal function precludes the use of aminoglycosides.[4] Interestingly, for all *Bartonella* spp. infections in people, overtly immunosuppressed patients have a more dramatic response to antibiotic therapy than immunocompetent individuals.[4]

Routine treatment of asymptomatic *Bartonella* spp.–infected cats is not recommended. True incidence of *Bartonella* spp.–induced disease is low, and indiscriminate antibiotic use may lead to resistance. In those cats with clinical signs suspected to be secondary to *Bartonella* spp., improvement or resolution of illness should be used to determine duration of therapy in conjunction with serial culture or PCR tests. Lack of response to appropriate anti–*Bartonella* spp. therapy should prompt clinicians to question whether the diagnosis of *Bartonella* spp.–induced disease is correct.

CONTROL AND PREVENTION

The only natural route of infection currently known is transmission by fleas during feeding.[18] Inoculation of flea feces into the bite lesion occurs either during feeding by the flea, or secondary to scratching or biting by the cat.[18] Based on studies of ectoparasites collected from dogs and nondomestic animals, ticks also are suspected to be capable of *Bartonella* spp. transmission.[2,79] Therefore, ectoparasite control is the most important method for preventing infection of naïve cats. Flea baths of seropositive cats immediately before introduction to a cattery without infected animals prevented seroconversion of the uninfected cats.[34] Limiting cat exposure to other animals, particularly stray cats or cats with access to the outdoors, is logical. However, unidentified factors may contribute to or prevent infection in cats; persistently infected animals within the same household may harbor different *Bartonella* spp. without cross-infection despite the presence of fleas.[80]

Zoonotic Considerations

Many of the syndromes caused by *Bartonella* spp. in human beings traditionally have been diseases of high-density populations with substandard hygiene or have been limited geographically by the distribution of the vector insect.[2,4] However, the increase in immunocompromised people throughout the world undoubtedly has contributed to the emergence of *Bartonella* spp. as an important zoonosis. Unfortunately the risk of transmission of bartonellosis from an infected cat to a person is unknown. At least one study showed that *B. henselae* seropositivity in human patients with a variety of conditions was not related to pet ownership.[81]

Based on identified risk factors for *Bartonella* spp. infection in cats, the ideal pet cat for an immunocompromised person is one raised in a clean, ectoparasite-free environment. Epidemiological studies have shown that cats greater than 1 year of age and cats that have been pets their entire lives are less likely to be seropositive or infected with *Bartonella* spp.* Therefore owners seeking a new pet should be counseled to adopt an adult cat from a private, cattery environment. Because the absence of anti–*Bartonella* spp. antibodies has a high negative predictive value, adoption of a seronegative cat is the best option. Owners should be warned however that even the use of antibody testing as a negative screening process will not completely eliminate infected cats, as a small number of cats are infected but seronegative. Blood culture or PCR can be used to confirm lack of infection if desired.

Any seropositive but non-bacteremic cat must be considered possibly infected, as bacteremia is cyclic. Theoretically, ownership of a seropositive or bacteremic cat with stringent ectoparasite control may decrease the risk of zoonotic transmission of *Bartonella* spp., because human infection also may require inoculation of flea feces. Treating seropositive or culture-positive cats with courses of antibiotics is of questionable value because elimination of the carrier state in cats has not been demonstrated definitively. Ultimately the decision on whether to recommend ownership of a *Bartonella* spp. seropositive or confirmed infected cat to an immunocompromised person is best left in the hands of a physician.

Blood Donor Testing

A consensus statement on appropriate screening of animals to be used as blood donors has been published by a panel of veterinary infectious disease experts within the American College of Veterinary Internal Medicine.[82] I recommend that practitioners or veterinary practices that are planning to establish their own cat blood donor pool follow these guidelines. Regardless, institutions that rely upon privately-owned volunteered cats for blood donors disagree on screening for *Bartonella* spp. infection. Given the high prevalence of infected cats, exclusion of seropositive or bacteremic animals significantly limits the available pool of blood donors. However, because experimentally infected cats are most likely to show clinical signs immediately after inoculation, it may be desirable to avoid transfusion of naïve ill patients as they may be unable to tolerate further insult. Maintenance of a *Bartonella* spp. seronegative donor pool may be feasible only in geographical regions of low seroprevalence.

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Chapter 5

Bacterial Causes of Enteritis and Colitis

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Bacteria probably are an important cause of enteritis and colitis in cats, although few studies have investigated the role of enteric bacteria in feline diarrhea. Determining whether the presence of a particular bacteria caused enteritis or colitis can be challenging, because many of these organisms exist as normal constituents of the indigenous intestinal flora. In addition, the isolation rates for putative bacterial enteropathogens often are similar in diarrheic and nondiarrheic cats, which makes a diagnosis of bacterial-associated diarrhea more difficult.

Based on the findings in other species, young kittens are assumed to be at greater risk than older cats for bacterial gastroenteritis. Younger patients also are more likely to have confounding factors (e.g., viral enteritis, parasites, dietary change) that make it easier for bacteria to cause clinical signs and at the same time more difficult to determine what actually is causing the disease. Clinical disease probably is often caused by the simultaneous presence of multiple factors, the sum of which prevents the intestines from being able to compensate.

This chapter first considers the various potential enteropathogens and then provides a summary of how to approach bacterial-associated enteritis or colitis in cats.

ESCHERICHIA COLI

A gram-negative facultative anaerobic rod of the family Enterobacteriaceae, *Escherichia coli* probably is the potential pathogen isolated most commonly from the gastrointestinal (GI) tract of cats (or any other species). *E. coli* is an expected commensal in the intestinal tract of cats; however, some strains have virulence factors that make them potential pathogens. Pathogenic *E. coli* in human beings and calves have been classified into different pathotypes based upon the mechanisms by which they cause disease. The naming of these pathogenic categories is not absolutely uniform, but most investigators classify pathogenic *E. coli* into the following categories:

1. Enterotoxigenic *E. coli* (ETEC), which produce heat-stable and/or heat-labile enterotoxins that cause disease via deregulation of the adenylate cyclase enzyme system and overproduction of cAMP with consequent loss of water and electrolytes into the intestinal lumen, leading to secretory diarrhea
2. Enteroinvasive *E. coli* (EIEC), which enter the intestines via M-cells and ultimately invade the enterocytes
3. *E. coli* that produce cytotoxic necrotizing factors (CNFEC)
4. Attaching and effacing *E. coli* (AEEC), which includes two subgroups: enteropathogenic *E. coli* (EPEC) and enterohemorrhagic *E. coli* (EHEC)

None of these groups have been shown to be major pathogens in cats. EIEC and ETEC are almost unreported in cats. Cytotoxic necrotizing factor–producing *E. coli* have been isolated from the intestines of normal cats but have not been shown to cause disease.[1]

EPEC carry a chromosomally located gene, *eae*A (*E. coli* attaching effacing), which allows them to attach to enterocytes and cause collapse of microvilli. EHEC are similar to the EPEC in that they attach to the enterocytes, but EHEC also produce a toxin that has been called Vero-toxin or Shiga-like toxin.[2] The EHEC includes the foodborne pathogen serotype O157:H7, an important strain that can cause hemolytic-uremic syndrome in people. EHEC tend to produce inflammatory lesions and hemorrhage and are seen more often in the colon.[3]

Feline small intestine has a glycosphingolipid that serves as a potential binding site for EHEC.[4] However, most feline EHEC isolates do not have the *eae* gene, which means that they are probably less virulent for cats.[5] AEEC have been reported in cats.[6] In one study, 5 per cent of 113 *E. coli* isolates from cats with diarrhea, enteritis, or septicemia were *eae*-positive.[6,7] In another study, 81 per cent of hemolytic and 18 per cent of nonhemolytic *E. coli* isolates were enteroaggregative, but none tested positive for Shiga-like toxin.[8] A study of 113 cats with diarrhea and 66 normal cats found about a 5 per cent prevalence in both groups, which does not prove clearly that EHEC

cause disease in cats. One report exists of a case of rhabdomyolysis associated with renal failure and *E. coli* gastroenteritis in a cat.[9] However, as is often the case, cause and effect is not clear cut, and the *E. coli* was not investigated for virulence factors that would make it a likely pathogen. Therefore, although EPEC and EHEC have been isolated from cats and seemingly could have been responsible for disease, it is not clear that they are significant pathogens.

Diagnosis

Because *E. coli* is a significant component of the commensal feline intestinal flora, isolation of the organism is not diagnostic nor does it allow differentiation between pathogenic and nonpathogenic strains. Culture enables the application of molecular techniques for detection of specific toxin genes among isolated organisms. Isolation of *E. coli* is relatively easy from fresh feces on selective media such as MacConkey's agar, which support growth of gram-negative bacteria. The simple fact that a strain of *E. coli* is hemolytic when isolated on blood agar does not mean that it carries one of the virulence factors, and the absence of hemolysis does not mean that it does not carry one of the virulence factors. Biochemical testing can be used to further characterize *E. coli* strains. For example, isolates that do not ferment sorbitol are more likely to be EHEC. ELISA testing can be used to detect heat-stable or heat-labile toxin production; however, PCR has become one of the most common methods for detection and differentiation of pathogenic strains of *E. coli*.

Therapy

If *E. coli* is suspected of causing disease in a cat, therapy depends on the severity of clinical signs and whether evidence exists of systemic involvement. If the patient has only gastrointestinal signs (i.e., diarrhea), then antibiotic therapy is controversial and theoretically has the potential to make clinical signs worse. Fluid and electrolyte therapy is useful in more severely affected patients to support the cat until the infection resolves spontaneously. If involvement is systemic (e.g., fever, neutrophilic leukocytosis), then antibiotic therapy may be considered. Aminoglycosides (e.g., amikacin), with or without β-lactam drugs (e.g., amoxicillin plus clavulanate), or enrofloxacin are reasonable choices for patients with suspected septicemia.

SALMONELLA SPECIES

Another gram-negative aerobic rod of the family Enterobacteriaceae, *Salmonella* spp., have been documented clearly to cause disease in cats. Although not a common commensal like *E. coli*, *Salmonella* spp. can be isolated from the feces of up to 18 per cent of clinically normal cats.[10] *Salmonella typhimurium* is the most common isolate from cats, although numerous other serovars have been reported. Transmission usually is oral (either food or fecal-oral), although ocular and transplacental routes also are reported. Feeding raw meat and exposure to birds and bird feces are other potential sources of infection.[11] Infected cats can shed *Salmonella* spp. in their feces for at least 14 weeks,[10] and although feline-to-human transmission is a concern, it is documented very rarely.[12] Cats also are reported to shed *Salmonella* spp. from their oral cavities, which means that feline grooming habits may lead to contamination of their hair coats, which again makes transmission to people possible.[13]

Salmonella spp. usually infect the host when they pass through the stomach in sufficient numbers to colonize and invade the ileal mucosa. Virulence depends upon the strain's ability to invade and multiply within the mucosa, but enterotoxins also may be important. Signs of disease depend upon the virulence of the strain and the host defense mechanisms. Anything that decreases normal bacterial populations in the intestines or decreases gastric acidity is believed to make colonization and disease more likely. One report suggested that the use of modified-live panleukopenia virus vaccine may have impaired the host defenses in a cattery, which resulted in fatal salmonellosis in at least one kitten.[14]

Cats infected with *Salmonella* spp. can show a plethora of signs, including conjunctivitis, abortion, or systemic signs of sepsis.[10,15] Many cats infected with *Salmonella* spp. also can be completely asymptomatic. Very young kittens and very old cats appear to be at increased risk for gastroenteritis. In addition, cats that are immunocompromised secondary to corticosteroid administration, chemotherapy, or retrovirus infection may be at increased risk for *Salmonella* spp. infection. Fever is common in infected cats, and nausea is not unexpected. Systemic illness may produce signs of sepsis, but very young cats may not be febrile despite being bacteremic.

Song bird fever is the name of a syndrome believed to be due to *S. typhimurium*. Reported in the northeastern United States, cats become infected when they are exposed to infected bird feces at feeding stations, or if they catch and eat birds carrying the organism. Fever, anorexia, vomiting, and diarrhea (often hemorrhagic) are common clinical signs.[16] A similar situation has been reported in Sweden,[17] in which *S. typhimurium* was isolated from the feces of anorexic cats that also evidenced vomiting (63 per cent), diarrhea (30 per cent), fever (89 per cent), and/or abdominal pain (97 per cent).

Diagnosis

The traditional diagnosis of feline salmonellosis is made based on isolation of the organism in conjunction with clinical signs and assessment of potential risk factors, such as hospitalization, age, environmental exposure, and antibiotic administration. Isolation of *Salmonella* spp. is not necessarily indicative of involvement in disease. Furthermore, failure to isolate *Salmonella* spp. from feces does not eliminate it as a possible cause of GI disease. Hematologic abnormalities are variable and include nonregenerative anemia, lymphopenia, thrombocytopenia, and neutropenia with a left shift. Toxic neutrophils can be found in cats with systemic disease and endotoxemia, findings similar to those documented with feline panleukopenia.

Salmonella spp. can be overgrown easily by other bacteria found commonly in feces; therefore fresh fecal specimens must be placed in an appropriate transport medium and then transported to a suitable laboratory as quickly as possible. Fecal specimens should be placed onto one or more selective media, including MacConkey's agar, XLD agar, and brilliant green agar. For enrichment, selenite F, tetrathionate, or gram-negative broth are recommended. The fact that using enrichment and selective media substantially enhances isolation of *Salmonella* spp. underscores the importance of notifying the laboratory as to which bacteria is being sought. In contrast,

growing *Salmonella* spp. from sites where it is not expected (e.g., blood, urine, bronchial secretions) usually is easier than isolation from feces, and also is definitive for the diagnosis of systemic salmonellosis. Systemic salmonellosis can be associated with GI salmonellosis.

Therapy

Cats with simple gastroenteritis associated with *Salmonella* spp. but with no signs of systemic disease purportedly do not need antibiotics. Antibiotic therapy has been hypothesized to promote development of drug resistance; however, this concept is now contested, and the optimal therapeutic approach to these patients is not clear. In contrast, cats believed to have salmonellosis that have signs of systemic infection (e.g., fever, toxic neutrophils) should be treated with systemic antibiotics. Sensitivity testing is preferred because some strains of *Salmonella* spp. grown from cats (e.g., DT 104) commonly are multidrug resistant.[13] In one study in England, 40 of 78 *S. typhimurium* isolates from cats were DT 104.[18] While waiting for sensitivity results, the clinician may initiate therapy with amoxicillin or a potentiated sulfa drug. Aminoglycosides and quinolones may be used in severely ill patients.

If salmonellosis is suspected, steps to prevent contagion to other cats and people are indicated. Zoonotic transmission is possible from infected cats, but the incidence probably is low. In Sweden, two cases were reported of suspected but unproven transmission of *Salmonella* spp. from cats to human beings.[17] Sodium hypochlorite and quaternary ammonium solutions used in appropriate concentrations and with sufficient surface contact time are effective disinfectants. Although effective, phenolic compounds are toxic to cats and should be avoided.

CLOSTRIDIUM PERFRINGENS

Clostridium perfringens is a gram-positive, obligate anaerobic rod that forms spores. The pathogenesis of *C. perfringens*–associated diarrhea has not been elucidated in cats to date. However, the disease most likely occurs secondary to disruption of the animal's commensal microflora in association with indiscriminate antimicrobial therapy, sudden change of diet, or intestinal disease, which results in massive sporulation of established vegetative organisms, with consequent release of enterotoxin or other virulence factors. As described for *E. coli* and *Salmonella* spp., *C. perfringens* can be isolated from feces of clinically normal cats.[19] *C. perfringens* enterotoxin (CPE), a 35-kDa protein encoded by the *cpe* gene, is believed to be one of the main virulence factors associated with diarrhea. CPE is produced in large quantities by enterotoxigenic strains during sporulation and then is released on lysis of the mother cell. However, other clostridial toxins (e.g., α toxin, β2 toxin) can cause intestinal disease, and it is not clear how often these other toxins are responsible for diarrhea.

Diagnosis

Clostridium perfringens often is ascribed as the cause of large bowel diarrhea; however, small bowel diarrhea or diffuse disease can occur. Patients with large bowel disease may have fecal blood and mucus, but many have neither. Diarrhea often is the only sign of disease; weight loss, vomiting, and anorexia are extremely uncommon. Culturing feces is not helpful in diagnosis of clostridial enteritis/colitis because the organism is a normal commensal and is isolated commonly from the feces of healthy cats. In addition, isolation studies are time consuming, relatively expensive because of the need for an anaerobic environment, and unable to differentiate between toxigenic and nontoxigenic strains.

Diagnosis traditionally has involved either detection of excessive numbers of spores in the feces during direct examination of a stained fecal smear or discovery of evidence of the clostridial enterotoxin in the feces. Fecal endospore counting is not reliable for diagnosing *C. perfringens*–associated diarrhea in dogs because no association exists between endospore counts and detection of CPE, or between endospore counts in diarrheic and nondiarrheic dogs. These findings have raised the same concerns with use of fecal endospore counts in cats for diagnosing *C. perfringens*–associated diarrhea.[20,21] Detecting CPE in the feces has been suggested as being the preferred means of diagnosis, and reports exist in which detection of CPE seemed to be useful.[19]

However, questions have arisen about the sensitivity and specificity of the various toxin assays available. The reversed passive latex agglutination (RPLA) test clearly is not as sensitive or specific as the ELISA and often is associated with a high incidence of false-positive results. In addition, results of the assay are difficult to interpret and require an overnight incubation process. For these reasons, we do not advocate the use of this assay for detecting CPE in cats. The currently recommended ELISA that is used for detection of CPE has not been validated to date in cats, and results could be altered (false-positive and false-negative) with delayed processing of fecal specimens.[21] Although having typical signs, excluding other causes, and seeing a prompt response to administration of an appropriate antibiotic is typically how a diagnosis of *C. perfringens*–associated diarrhea is made in cats, veterinarians must not overinterpret a positive response to antimicrobial therapy. There are many reasons why a diarrheic cat not affected with *C. perfringens* might "respond" to metronidazole administration. Finding CPE in the feces by ELISA strengthens the diagnosis; however, the diagnosis should not be excluded based on a negative ELISA result.

Therapy

C. perfringens usually is sensitive to tylosin or amoxicillin, and most affected animals show amelioration of clinical signs within 1 to 3 days of initiation of one of these drugs. Metronidazole typically is effective *in vitro*, but we have seen cases in which therapy apparently failed *in vivo*, possibly because of inadequate concentrations of the drug in the feces.[22] If the patient responds to such therapy, administration of the antibiotic should continue for another 10 to 14 days. If relapse occurs while the patient is still receiving amoxicillin or tylosin, then it is more likely that *C. perfringens* was never the cause of the diarrhea rather than *C. perfringens* becoming resistant to these antibiotics. Chronic diarrheas may wax and wane, and the clinician must be careful about ascribing cause and effect too soon after therapy is initiated.

If the clinician decides that antibiotics are responsible for clinical improvement in a cat with large bowel diarrhea, the clinician may try adding a fermentable fiber source such as psyllium to the diet in the hopes that if it works, the antibiotics may be discontinued eventually. Some tylosin- or amoxicillin-

responsive large bowel diarrheas can be controlled by adding a fermentable fiber source to the diet, possibly because the fiber alters the fecal microenvironment such that toxin production is less likely. This is pure conjecture, but the treatment seems to work in a number of patients.

CLOSTRIDIUM DIFFICILE

Clostridium difficile is a gram-positive, anaerobic spore-forming rod. The disease probably is spread by the fecal-oral route, with the environmentally resistant spores being the most likely means of transmission. Transmission within hospital wards is prevalent because of the resistance of the spores to common disinfectants. *C. difficile* is a major cause of antibiotic-associated diarrhea in human beings and has been well described as a cause of pseudomembranous colitis, which occurs classically in people receiving clindamycin, penicillins, cephalosporins, or other antibiotics. When conditions are optimal (usually because of disruption of the commensal colonic flora resulting from antibiotics), toxigenic *C. difficile* proliferates and produces toxin A (enterotoxin) and/or toxin B (cytotoxin), which causes cellular disruption, necrosis, and diarrhea.

In one study, 38 per cent of 21 cats had *C. difficile* isolated from their feces.[23] However, details regarding clinical signs were not given. In another study at a veterinary teaching hospital in the United States, 23 of 189 in-patient cats were found to shed *C. difficile* in the feces, and 8 of these 23 cats were carrying toxigenic strains.[24] All of these cats had at least one identifiable factor considered a risk factor in people for *C. difficile* colonization (e.g., antibiotic use). In contrast, none of 49 research cats nor 56 healthy cats from an outpatient clinic were found to shed *C. difficile*.[24] Other studies have found carriage rates of 2 per cent (New Zealand) and 39 per cent (Australia).[24]

Diagnosis

Few reports exist of suspected *C. difficile* infection causing diarrhea in cats[25]; therefore meaningful characterization is difficult of the typical diarrhea expected from feline *C. difficile* infection. As with *C. perfringens*, isolation of *C. difficile* from diarrheic specimens is of little diagnostic value, except for procuring strains for detection of toxin genes and typing. Fecal isolation of *C. difficile* can be somewhat useful, however, because it is extremely unlikely for a cat to have *C. difficile*–associated diarrhea with a negative fecal culture. Diagnosis of *C. difficile*–associated diarrhea traditionally has been made based on positive fecal assays for toxin A or toxin B. All currently used ELISA assays for detection of toxins are marketed for human testing, and the performance characteristics of these assays have not been validated in cats to date. Cats with *C. difficile*–associated diarrhea invariably are positive for toxin A, although toxin A-negative/toxin B-positive strains plausibly could exist, similar to findings in human beings. Completely ruling out a diagnosis of *C. difficile*–associated diarrhea is impossible on the basis of a negative ELISA test that evaluates for the presence of toxin A only. Several available commercial ELISA kits test for the presence of toxin A and B concurrently.

C. difficile should be considered a potential cause of disease if evidence exists of a contagious diarrhea, or if diarrhea began after antibiotic therapy was initiated. These factors do not allow a presumptive diagnosis of *C. difficile*–induced diarrhea, but they should arouse suspicion.

Therapy

If *C. difficile* is suspected as a cause of diarrhea, then metronidazole is considered to be the drug of choice. Vancomycin also is effective in treating this disease, but its use must be limited to cats resistant to metronidazole. Vancomycin currently is the only antibiotic to which some strains of *S. aureus* affecting human beings are susceptible. The overuse or inappropriate use of vancomycin may induce more strains of vancomycin-resistant *Staphylococcus* with a potentially catastrophic impact on human health care.

CAMPYLOBACTER SPECIES

Campylobacter spp. are microaerophilic gram-negative curved rods of the family Campylobacteracea. Similar to the previously discussed bacteria, *Campylobacter* spp. also can be isolated from the feces of normal and diarrheic cats. Fecal-oral transmission is likely, but food may be the source of infection in people, especially improperly prepared poultry products. Many species of *Campylobacter* have been isolated from human beings and cats; however, *C. jejuni* and *C. coli* probably are the species that are recognized most often as being potentially pathogenic in people. In fact, *C. jejuni* recently has been implicated as a cause of immunoproliferative small intestinal disease in human patients.[26] However, *Campylobacter upsaliensis* has been identified recently as a potential pathogen in human beings, and in many studies this species is isolated from cats as frequently or more frequently than *C. jejuni*.[27] In one study in the United Kingdom, 60 per cent of clinically normal cats shed *C. upsaliensis* in their feces,[28] whereas 50 per cent of all *Campylobacter* spp. isolated from cats in another study in Switzerland were *C. upsaliensis.*[29] In contrast, only 1 to 10 per cent of cats typically are found to be shedding *C. jejuni.*[30] *Campylobacter helveticus* also has been isolated from feline feces, but no evidence exists that it causes disease in cats.

Campylobacter spp. generally cause disease by invading the epithelium in the distal small bowel and the colon where they produce cytotoxins and/or enterotoxins. Clinical signs include mucus-laden or watery diarrhea (with or without blood and leukocytes), partial anorexia, occasional vomiting, and slight fever of 3 to 7 days' duration. Concurrent infection with other enteric pathogens such as feline panleukopenia virus, *Giardia* spp., or *Salmonella* spp. may play a synergistic role and worsen the clinical signs.

Although recognized as a well-established cause of enteritis in human beings, *Campylobacter* spp. are not clearly an important cause of feline gastroenteritis. One recent study reported that no difference exists in the prevalence rates of *Campylobacter* spp. infections in healthy cats and diarrheic cats,[31] and investigations in one of the author's laboratory (SLM) commonly have yielded higher isolation rates of *Campylobacter* spp. in healthy cats compared with diarrheic cats.

Diagnosis

Campylobacter-like organisms (CLOs) can be identified by examining stained smears (Gram stain or Romanovsky type stain) of fresh feces from cats. *Campylobacter* spp. typically have a characteristic S-shaped or a seagull wing–shaped

appearance that allows them to be identified relatively easily. However, other bacteria such as *Helicobacter* spp. and *Anaerobiospirillum* spp. may have a similar appearance. Identification of CLOs is not sufficient to warrant a diagnosis of *Campylobacter*-associated diarrhea, because many healthy cats can harbor CLOs in their intestinal tract.

For optimal recovery of *Campylobacter* spp., feces or swabs should be fresh or refrigerated at 4° C. Swabs should be placed immediately into anaerobic transport medium before refrigeration. For isolation, the use of a formulated selective medium containing antimicrobial agents (e.g., Campy-CVA containing cefoperazone, vancomycin, and amphotericin B) gives better recovery than other direct-plating selective media. Optimal microaerophilic incubation conditions for isolation are 5 per cent oxygen, 10 per cent carbon dioxide, and 85 per cent nitrogen, achieved by use of commercially available packs (Pack Campylo AnaeroPack System, Mitsubishi Gas Chemical Company, Tokyo, Japan). The plates should be incubated at 37º C or at 42º C when isolation of *C. jejuni* and *C. coli* from feces is attempted. Suspect colonies should be Gram stained and subcultured to 5 per cent sheep blood agar (SBA). Biochemical tests then are performed to separate all CLOs isolated. Phenotypic tests can provide unreliable identification and further testing usually is warranted. PCR technology has become virtually standard operating procedure to identify thermophilic *Campylobacter* spp. samples from different animal species.

Therapy

If campylobacteriosis is suspected strongly, then erythromycin is one of the most consistently effective antibiotics for *C. jejuni*. Tetracyclines most likely are the next best class of antibiotics to use for *C. jejuni* and probably are more likely to be effective against *C. upsaliensis*.[27] Although the quinolones (enrofloxacin) usually are effective for the eradication of *Campylobacter* spp., *Campylobacter* spp. have a high rate of mutational resistance to the quinolones. Therefore judicious use of this class of drugs is warranted. β-Lactam drugs are seldom effective. Administration of erythromycin does not clearly shorten the length of clinical signs in human patients but does seem to lessen the length and severity of fecal shedding.[21]

Human beings are relatively susceptible to some strains of *Campylobacter* spp., and transmission from cats to people has been reported.[30] This probably is due in part to the fact that relatively few organisms are required to establish infection in human beings. Infected cats can shed the bacteria for 4 months. Young children probably are at greatest risk for being infected by cats.

ANAEROBIOSPIRILLUM SPECIES

These are motile, spiral-shaped, gram-negative, anaerobic rods. This genus is recognized as a normal commensal in the feline intestinal tract.[32] These bacteria often can be seen on direct fecal smears, especially in diarrheic patients. They have been identified as a cause of septicemia in immunocompromised human beings and have been isolated from healthy cats. Ileocolitis associated with *Anaerobiospirillum* spp. was found in six cats recently. Three cats were presented with gastrointestinal signs characterized by vomiting or diarrhea, one cat was presented with an acute onset of anorexia and lethargy, and two cats had no clinical or systemic signs related to the gastrointestinal tract.[33] Cause and effect was suspected; however, controlled challenge infection of susceptible cats with feline *Anaerobiospirillum* spp., coupled with detailed pathological investigations, is needed to confirm the enteropathogenicity of *Anaerobiospirillum* spp., which is associated with feline enterocolitis.

HELICOBACTER SPECIES

Although most of the interest in *Helicobacter* spp. has centered on gastric *Helicobacter* spp., isolates from this genus have been cultured from feces of cats. A few reports exist of *Helicobacter* spp. being isolated from cats with diarrhea. The first report was of *Helicobacter colifelis* being grown from the lower intestinal tract of a cat.[34] Another report describes *Helicobacter canis* cultured from the feces of four Bengal cats.[35] These were from a cattery with 20 other cats, 75 per cent of which had episodic diarrhea that was characterized as being watery, mucoid, and/or blood tinged. However, other potential GI pathogens (i.e., *C. helveticus*, *C. perfringens*, and *C. difficile*) also were cultured from these cats, and some of the nondiarrheic cats were found to have *H. canis* in their feces too. Therefore cause and effect is hard to ascribe. Finally, a *Flexispira rappini*–like organism (a type of *Helicobacter* spp.) was grown from a 4-month-old kitten that died of hemorrhagic enteritis.[36] Coinfections with *Helicobacter* and *Campylobacter* spp. may be more common than suspected, and distinguishing between these two genera can be difficult. PCR is necessary to characterize isolates accurately.[30]

APPROACH TO APPARENT BACTERIAL GASTROENTEROCOLITIS

Almost any cat with gastroenteritis may have a bacterial cause. However, finding disease in young kittens, having signs begin after initiating antibiotic therapy, and/or a history suggestive of contagion seem especially suggestive of bacterial gastroenterocolitis. No clearly proven breed predispositions exist, although Bengal cats anecdotally might be at greater risk. Diagnostic tests may reasonably include checking for concurrent problems that would make management more difficult (i.e., FeLV and FIV infection, intestinal parasites). Although fecal cytology for identification of bacteria is inexpensive, the study is nonspecific, and caution is warranted to avoid overinterpretation of the findings of bacterial endospores or spiral-shaped bacteria suggestive of CLOs. In general, supportive care (i.e., fluid therapy, antiemetics, nutritional support) and good hygiene usually are the most important aspects of therapy. If no evidence exists of systemic infection, then antibiotic therapy is of questionable value. However, if evidence exists of systemic disease (e.g., fever, depression), parenterally administered systemic antibiotics seem reasonable. Although diarrhea produced by *Campylobacter* organisms usually is self-limiting, the zoonotic potential of the organism often necessitates medical therapy.

When only one cat is involved, attempts to isolate putative pathogenic bacteria are seldom necessary or appropriate, unless the patient is nonresponsive to therapy that would have been expected to be effective. However, an epidemiological problem with multiple animals (or people) involved typically would warrant an attempt to identify any causative bacteria. The

laboratory should be contacted before samples are collected to find out exactly what is required. In general, the clinician must obtain fecal samples that are as fresh as possible and transport them to a microbiology laboratory well acquainted with fecal culture techniques and toxin assays (not every microbiology lab is) as quickly as possible using appropriate transport media. Furthermore, culturing several animals in early stages of the disease typically is best. Finally, the lab must know which bacteria are suspected to be causing disease.

In general, to properly culture feces from a group of animals with gastroenteritis is a time-consuming, expensive process that often yields equivocal results. Therefore it should be done only when clearly necessary because of epidemiological concerns or failure of seemingly appropriate therapy.

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Chapter 6

New Diagnostic Tools for Infectious Disease

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Diseases caused by infectious agents are frequent in veterinary medicine. The signalment, history, and a thorough physical examination lead the clinician to suspect that an infectious disease may be present and lay the foundation for development of a differential diagnosis list and choice of the appropriate laboratory tests. Clinical signs associated with infectious disease can be varied and depend on the infecting agent and the organ system involved.

The first step in the laboratory evaluation is to establish a minimum database, including a complete blood count, serum biochemistry panel, and urinalysis. This minimum database, along with ancillary diagnostics such as radiographic imaging, aids in identifying specific organ involvement and can lead to a presumptive diagnosis that an infectious disease is present. Further testing often is required to identify specifically which infectious agent is involved to determine an appropriate treatment plan for the patient. This chapter discusses the laboratory tools available for infectious agent identification.

Laboratory diagnostic tools can be divided into two main categories: (1) direct identification of the infecting agent/antigen (Table 6-1), and (2) indirect identification by detection of antibodies directed specifically against the infecting agent/antigen (Table 6-2).

IDENTIFICATION OF ANTIGEN

The most common laboratory methodologies used to identify an infectious agent include visualization of the organism via cytology/biopsy, isolation of the agent in microbiological culture, immunodiagnostics/serology, and nucleic acid technology.

Cytology

Cytology is the fastest and most inexpensive way to identify the presence of an infectious organism. Microscopic examination of body fluids, fine-needle aspirates of solid organs, and imprints or scrapings of superficial lesions are just a few examples of ways in which infectious agents can be collected and identified morphologically. One of the limitations of cytology is whether the organism occurs in sufficient numbers in circulation or in the tissues or fluids to be identified. To help identify low numbers of organisms, intracellular organisms, and viruses, special stains with affinities for certain physical characteristics of the agents can be applied to the cytology sample. Routine special stains include Gram stain, periodic acid-Schiff (PAS), and acid-fast stain.

Immunohistochemistry

A major advance in cytology over the years has been the development of immunocytochemistry. This methodology uses agent-specific polyclonal or monoclonal antibodies that react with unique antigens on various pathogenic organisms. The resulting antibody-antigen complexes then are detected by either fluorochromes that emit fluorescence or a chromogen that provides a color change. For example, anticoronavirus antibodies can be applied to fluid samples or granuloma aspirates from cats with suspected feline infectious peritonitis to detect the presence of coronavirus within macrophages or monocytes in the sample.

Immunohistochemistry is used classically to characterize and identify tumors for prognosis or to identify markers for therapeutic intervention, and also can be used for organism identification. Polyclonal anti–*Mycobacterium bovis* antibody has been shown useful as a single screening method for the detection of a number of different microorganisms in skin biopsies.[1]

Cytology and biopsy samples also can be used as a source for cells, DNA, and RNA extraction. Cells and organisms can be extracted from cytology slides, formalinized tissue, and paraffin-embedded tissue and then evaluated via flow cytometry with immunomarkers or polymerase chain reaction (PCR).[2] As more antibodies are made available, the menu of organisms that can be identified will expand. These techniques are offered at many universities and reference laboratories.

Microbiological Culture

Microbiological culture typically is performed to identify bacterial or fungal organisms. Challenges associated with culture

Table 6-1 | **Categorization of Antigen Detection Methods**

TECHNIQUE	TARGET	ADVANTAGES	DISADVANTAGES	EXAMPLE	NEW ADVANCES	COMMENTS
Cytology/biopsy	Whole organism	Fast, inexpensive, highly specific	Organism may not be in sample collected; training required to evaluate sample; labor-intensive	*Histoplasma capsulatum* in lung aspirate	Immunostaining, flow cytometry	Negative test does not rule out infection.
Microbiology	Whole organism	24–48 hr; can provide antimicrobial susceptibility; possible to perform indirect measurement of growth (gas production)	Limited by the growth traits of the organism (i.e., intracellular, fastidious, slow growth)	*Salmonella*, *Mycobacterium* spp.	Automation	Testing is limited to readily culturable organisms; cannot be used for viruses.
ELISA	Surface antigen, peptide	Easy to perform; rapid results; inexpensive; highly sensitive; patient-side testing available		FeLV, *Dirofilaria*, *Giardia* spp.	Molecular techniques for development of highly specific monoclonal antibodies	Substrate (blood, feces) differs depending on the organism.
Latex agglutination	Surface antigen	Easy to perform; rapid results; inexpensive		*Cryptococcus neoformans*		Negative test does not rule out infection.
PCR	Nucleic acid sequence	Sensitive and specific; can detect minute amounts of DNA and RNA	Can detect residual organisms that are dead after successful treatment	*Ehrlichia canis*, FIV	Assay formats and equipment that minimize contamination and provide substantiating information (amplicon melting temperatures)	False negatives because of inhibitors; false positives because of contamination can occur; no established quality control protocols.

include adequate sample collection, biological behavior of the organism, and interpretation of the results. The first challenge is collection of the specimen. The affected organ may not be readily accessible and the sample must be collected without contamination. At the laboratory, the great diversity of infectious microorganisms and their varied biological behaviors can make accurate identification difficult. To help overcome these challenges, many microbiology laboratories now use automated systems that can run a wider range of biological tests and compare the behavior of the sample organism on these tests with a database containing information about the reaction patterns of known pathogens. With the addition of more tests and computer algorithms to compare with a large database, the probability of correct identification of the organism is increased.

Once identified, the susceptibility of the organism to numerous antimicrobial agents can be determined. Laboratories now routinely provide the minimum inhibitory concentration (MIC), which is defined as the lowest concentration of the antimicrobial drug that inhibits the growth of the organism. These values then can be compared with the levels attainable in serum or tissue to determine the most appropriate antimicrobial agent for the treatment of that particular organism in that particular site.

Some new assays combine culture and cytology. For example the InPouch TV culture system by BioMed Diagnostics (White City, OR) for the identification of *Tritrichomonas* spp. uses a clear pouch containing culture media to increase low numbers of organisms rapidly in a sample. The sealed pouch then is placed directly on a microscope for reading (see Figure 15-2). The advantages of this system include less likelihood of contamination of the sample, reduced exposure of laboratory staff to a zoonotic organism, long shelf life of the culture system, and improved sensitivity compared with wet-mount preparations.

Fastidious, intracellular, and viral organisms do not lend themselves readily to growth-based technologies, and cytological detection is limited by the shedding characteristics and intracellular location of some agents. Whole organisms or their antigens can be detected immunologically in a wide range of specimens including serum, whole blood, feces, cerebrospinal fluid, body cavity effusions, synovial fluid, cell aspirates, and tissue samples. Because these assays are directed toward an antigen of the infectious organism, they usually are not species-specific and reagents from human assays often can be used on feline samples. However, when reagents validated for human assays are used, they should be revalidated with feline samples to ensure that interfering factors or cross-reactive antibodies are not present.

Immunodiagnostic Assays

Immunodiagnostic assays include fluorescent antibody (IFA), enzyme-linked immunosorbent assay (ELISA), latex agglutination, and immunoblotting. Fluorescent antibody and

Table 6-2 | **Categorization of Antibody Detection Methods**

TECHNIQUE	TARGET	ADVANTAGES	DISADVANTAGES	EXAMPLE	NEW ADVANCES	COMMENTS
Indirect immunofluorescence antibody assay (IFA)	Virus and whole cell	Visualization of target enables specificity	Cross-reaction with antibodies directed against similar organisms	FeLV		Negative test does not rule out infection; less sensitive than some ELISA or PCR tests
Complement fixation (CF)	Specific antigen	Detects antibody to a specific antigen	Complex test materials	*Histoplasma* spp.		Limited application
Hemagglutination (HA) and hemagglutination inhibition (HI)	Virus	Specific to virus of interest	Complex test materials; inhibitory factors can influence accuracy	Parvovirus		Not applicable to nonviral diseases
Serum virus neutralization (SVN)	Virus	Specific to virus of interest	Complex test materials	Calicivirus		Not applicable to nonviral diseases
Radioimmunoprecipitation (RIPA)	Specific antigens	Highly specific	Uses radioisotopes	FIV		Typically used for confirmation after a positive result with another method
Western blot	Fractionated lysate	Visualization and preliminary identification of specific antigen	Labor intensive	FIV		Cannot differentiate vaccine-induced antibody from antibody generated by true infection
ELISA	Lysate or specific antigens	Easy to use, easy to detect, in-clinic, reference lab		Lyme	Improved target antigens increase test accuracy	For some agents, tests differentiate antibodies generated by infection from those produced by vaccination

immunoblot assays are performed in commercial laboratories, whereas numerous patient-side rapid ELISA and latex agglutination kits are available for antigen detection. The antigen ELISA assay comprises capturing the antigen of interest by using an antibody immobilized on a solid phase (e.g., a microtiter plate, a membrane, or microparticles) and forming a sandwich with a second antibody that is coupled to an enzyme. Formation of this sandwich occurs only if the corresponding antigen is present in the sample. After binding, the enzyme is catalyzed to give a color reaction. The most widely used ELISA for antigen determination in cats is the feline leukemia virus (FeLV) antigen assay. As with other antigen serology assays, this technique is limited based on the level of antigen load, the location of the antigen (i.e., intracellular or extracellular), and cross-reactivity with other antigens. Recent advances in ELISA assays have been directed toward improving the specificity of the antibody to the organism in question or enhancements in the detection system. Initially, nonspecific, outer surface proteins were used to develop the assay antibodies. This often resulted in cross-reactivity with multiple organisms and false-positive test results. Many tests now use purified, unique proteins to produce highly specific antibodies for the assays. These improved tests have a high diagnostic sensitivity and specificity (greater than 95 per cent) and often are discordant with less specific whole-cell IFA tests.[3,4] Additional improvements in ELISA diagnostic assays include enhancements to the conjugate that allow shorter incubation times, superior reaction detection through the use of enzyme stabilizers, and longer conjugate stability and shelf life. Some detection systems have been changed to a non–enzyme-based conjugate for color detection using colloidal gold or colloidal carbon.[5]

Latex agglutination assays use latex microspheres coated with specific antibodies directed against an infectious agent. If the organism or antigen is present, the antibody-coated particles bind to the organism and cause agglutination. Latex agglutination tests are available for *Cryptococcus neoformans*, *Toxoplasma gondii*, *Histoplasma capsulatum*, and S*porothrix schenckii,* in addition to numerous bacterial pathogens.

Nucleic Acid–Based Testing

One of the most rapidly expanding areas of organism identification and antigen detection has been in the area of nucleic acid–based testing. Until the introduction of nucleic acid amplification by the PCR, detection of an organism's DNA or RNA

often was impossible because of the small amount of antigen present in a sample. PCR technology takes advantage of the normal function of polymerase enzymes. These enzymes are present in all living things and are responsible for copying, proofreading, and correcting errors in genetic material. Polymerase enzymes "photocopy" or amplify minute quantities of genetic material to a volume sufficient for it to be detected. To have a useful PCR assay, a nucleic acid sequence unique to a particular organism or class of organisms must be identified. This unique sequence is the material amplified and detected if the organism in question is present in the sample.

During the first step, DNA is extracted carefully from the sample containing the suspected infectious agent. The extracted DNA then is heat-stressed to cause it to uncoil from its normal double-helix structure and separate into individual strands. The second step involves the addition of the two unique primers that flank each side of the sequence of interest. The primers aid in identification and amplification of the unique DNA sequence in question. When the primer finds the matching section of nucleic acid sequence, this sequence is copied to produce a small fragment of DNA (the amplicon) specific to the organism. This series of steps is repeated 20 to 50 times, with the product of each round serving as additional template for subsequent rounds of amplification. The final result is a logarithmic amplification of the original nucleic acid sequence. Detection of the multiplied nucleic acid sequence is performed during the amplification process with fluorescence emission with each amplification step (real-time PCR), after the completion of all amplification steps with the use of a secondary detection method, or from electrophoretic separation of the final DNA fragment and detection by application of a labeled complimentary nucleic acid probe.

PCR has opened a new spectrum of infectious disease tests, and numerous laboratories have started offering PCR tests for veterinary pathogens. The challenges faced today are not technological but in establishing a standardized process for accuracy, reproducibility, and quality control of such a sensitive and powerful assay. PCR testing is being offered at an increasing number of facilities. However, few laboratories have provided the important validation data that are necessary to evaluate and compare methods for diagnostic accuracy. The absence of standardization in testing protocols, primer selection, laboratory contamination control measures, quality control monitoring, and validation methods has led to increasing lab-to-lab variability and poor lot-to-lot reproducibility. Until protocols are defined and universally standardized for PCR among laboratories, the clinician should request information regarding quality control testing and controlled data supporting the primers in use at that specific laboratory.

The introduction of PCR also has opened the door for another area of debate: the issue of whether infection necessarily means "disease." The ability of PCR technology to detect very small numbers of organisms has led some to consider the level of infection required to overcome the body's immune response and cause disease, suggesting that the organism detected by PCR may not always be the infectious agent causing the animal's current illness. This is further complicated by the fact that PCR cannot distinguish between viable and nonviable organisms, reinforcing the need to establish a comprehensive clinical profile in diagnosis. In addition, diagnostic guidelines must be established to aid in determining how many organisms are needed to cause disease, or additional data must be generated to better understand the rate of clearance of infectious agents after effective treatment.

Unlike the other methods discussed, PCR testing essentially is limited to reference laboratory testing because of the complexity of the materials, equipment, and technique, and the lack of an in-clinic PCR device. However, like ELISA and other previously complex methods, new technology eventually will provide in-clinic PCR capability, accompanied by standardized methods.

DETECTION OF ANTIBODY

Identification of the organism always has been the gold standard for diagnosing an infectious disease. However, because many organisms elude detection because of their small numbers or occult location within the body, direct identification of the organism is not always possible. Recent advances have extended the range of direct antigen detection (see discussion above on PCR). However, reliance on the detection of antibody in the serum as an indirect method for diagnosing many infectious diseases is prevalent. The methods for detecting antibody include ELISA, IFA, complement fixation (CF), hemagglutination inhibition (HI), serum virus neutralization (SVN), and Western blot analysis.

ELISA and IFA Antibody Assays

In the ELISA and IFA antibody assays, a specific antigen from the infectious agent in question is fixed to a solid surface (microtiter plate or glass slide, respectively) and the patient's serum is added. If antibodies to this organism are present in the patient's serum, they will bind to the antigen. An enzyme-conjugated or fluorescent-labeled anti-species antibody then is used to detect the bound antibody. Commercial laboratories usually use antigen bound to microwell plates. Membrane-bound antibody is used in the small, self-contained in-clinic test kits used by most veterinary hospitals. A fluorescent microscope and trained technicians are required to perform IFA testing and these tests are available only in commercial laboratories.

Hemagglutination Inhibition Test

The hemagglutination inhibition test is used to detect antibody against some viruses that possess a hemagglutinating antigen (HA), which is capable of agglutinating erythrocytes. The HA is placed in a microtiter well and incubated with the patient's serum. If virus-specific antibodies are present in the test serum, they will bind to HA and prevent agglutination of erythrocytes added in the last step. Unfortunately, some serum samples have interfering factors that bind to HA and produce false-positive results. In addition, the HA may have varying affinities for different species of erythrocytes and produce different results with sheep, rabbit, mouse, or guinea pig red blood cells.

Serum Virus Neutralization and Complement Fixation Assays

Serum virus neutralization (SVN) and complement fixation (CF) assays determine whether antibody is present by evaluating some normal immunoglobulin functions. The SVN assay evaluates the ability of antibodies in a patient's serum to

prevent the infection of culture cells or embryonated eggs with a known specific virus. The patient's serum first is inoculated with the virus. Then the virus-serum mixture is injected into a cell culture to detect virus infectivity. Virus-specific antibodies in the patient's serum inactivate the virus and prevent infection of the cells. The CF assay assesses the ability of antibodies to bind to a specific antigen and complement to form an antigen-antibody-complement complex. This complex ties up the complement and prevents it from lysing red blood cells added as a substrate. Complement fixation assays also can be used to detect antigen.

Test Limitations

All of the antibody tests discussed so far measure antibody to whole cell antigens or viruses. The Western blot assay separates the infectious agent into its composite proteins by gel electrophoresis. The proteins are transferred to blot paper and are incubated with the patient's serum. If antibodies to virus-specific proteins are present, they will bind to the protein bands on the blot paper and can be detected by a labeled secondary anti-species antibody. Antibody binding to a combination of bands usually is required to confirm a diagnosis.

The main limitation of using antibody detection for diagnosis is that, in most diseases, the presence of antibody against an infectious agent cannot differentiate among patients with previous exposure having lingering antibodies, patients with current active infection, or patients with antibodies generated by previous vaccination. Until the recent release of a whole virus vaccine against feline immunodeficiency virus (FIV), the presence of serum antibodies against FIV was definitive proof of infection because virus-infected cats remain persistently infected for life. Unfortunately, antibodies produced in response to this whole virus FIV vaccine are indistinguishable from antibodies generated by true FIV infection and are detected with all FIV antibody assays (IFA, ELISA, and Western blot). This severely limits the utility of FIV antibody detection in FIV-vaccinated cats.

To combat this type of interference, researchers are looking for antibodies produced in response to infection but not as a result of immunization. For some pathogens, antibodies have been identified that are directed against specific proteins that are present only on the organism when it is alive within the host.[4] New assays use these live-pathogen specific peptides instead of whole cell proteins to detect antibodies directed only against those specific peptides. An example of this type of peptide is the recently identified invariable, immunodominant region (IR_6) on a variable region of the lipoprotein (VlsE) of *Borrelia burgdorferi*.[6] The IR_6 peptide is highly antigenic and stimulates antibody production that rises rapidly during experimental infection and drops rapidly with successful treatment. Several theories have been proposed to explain this phenomenon, including the possibility that the variable region of the VlsE protein is changed rapidly in the organism and older variant molecules are degraded rapidly. This high turnover rate also would ensure that the protein would be rare in dead organisms.[7] Therefore acute infections treated immediately showed a rapid rise and drop in antibody against this antigen. It has yet to be determined whether antibody levels in chronic cases will respond similarly, and whether the IR_6 is exposed to memory cells over time, resulting in antibody levels that persist following infection and treatment. Vaccination against *Borrelia* spp. apparently does not induce antibodies to IR_6, because the DNA that encodes the IR_6 sequence is not present in the laboratory strains of *B. burgdorferi* used for vaccine production.[8]

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Chapter 8

Localized and Generalized Tetanus

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In the current age of readily available, sophisticated diagnostic tools, the art of pattern recognition sometimes is frowned upon or forgotten. Yet the presence of a characteristic set of physical findings is all that is required to establish a diagnosis of tetanus in cats. A definitive diagnosis is relatively difficult to prove, but the distinctive pattern of rigidity starting in one limb or other localized muscle groups is virtually pathognomonic. Tetanus is relatively rare in cats as a result of their innate resistance to tetanus toxin.[1,2] Factors that contribute to this innate resistance are likely to account for the localization of the disease in many instances. With appropriate management, all cats eventually return to normal. Treatment of cats with generalized tetanus is more challenging and intensive than cases with localized tetanus, but most patients can be saved with diligent care.

ETIOLOGY

Tetanus is caused by the action of the extremely potent neurotoxin, tetanus neurotoxin (TeNT) or tetanospasmin, produced by the vegetative form of *Clostridium tetani*.[2,3] Spores produced by these gram-positive, anaerobic, nonencapsulated bacilli enable them to survive adverse conditions and are therefore ubiquitous in soil, dust, and the intestinal contents of numerous animal species. The vegetative form of *C. tetani* is no more resistant to disinfection, heat, or pH than other organisms, whereas the spores are particularly resistant to both adverse environmental conditions and routine disinfection. However, autoclaving at 121° C for 20 minutes for unwrapped items and 30 minutes for wrapped items ensures the sterility of materials used for surgery.[4,5] Spores gain access to the body via penetrating trauma (which may be minor) that provides suitable anaerobic environmental conditions for them to germinate. Growth and multiplication of relatively small amounts of *C. tetani* after germination and the production of tetanospasmin lead to the manifestation of clinical signs.

EPIDEMIOLOGY

Table 8-1 provides a summary of all 41 available reports of tetanus in cats.[6-37] The ubiquitous nature of *C. tetani* has led to a worldwide distribution of tetanus in cats and all other susceptible animal species. Typically, traumatic injury creates the portal of entry for the clostridial spores in most animal species, including cats. Of the 28 reported cases in which traumatic injury was a known inciting cause, the nature of this trauma was as follows: deep penetrating wounds (15 cases),* limb caught within hunting traps (eight cases),† compound bone fractures (four cases),[20,29,31,37] skin ulcers resulting from chemical burns (one case),[25] and skin abrasions secondary to vehicular trauma (one case).[35] In developed countries, despite the widespread availability of vaccines, tetanus in human beings is seen most commonly in the elderly, and the bacterial spores are thought to enter via skin ulcers or minor abrasions similar to the latter two cases noted.[38] The December 2004 South-East Asian tsunami resulted in more than 100 reported cases in human beings. It is likely that clostridial spores gained entry into the wounds of this unvaccinated population as they waded through the contaminated mud.

The high frequency of misadventure as a precipitating cause of tetanus in cats may explain the overrepresentation of the male gender (24 of 38 reported cases in which gender is noted), because males are more likely to wander and become injured. In addition, the more active and dangerous lifestyles of younger cats may explain the high frequency of young cats with tetanus, because only five cats were older than 4 years of age. However, external penetrating trauma is not the only cause of feline tetanus. In 10 of the 41 reported cases, ovariohysterectomy (four cases)[27,28,36] or castration (six cases)‡ appears to have provided the opportunity for spores to germinate in tissues disrupted by surgery. In one cat, *C. tetani* was isolated from a hunting trap wound in addition to the scrotum after castration at the time of limb amputation.[10] No breed predisposition was apparent.

Before the seminal paper in 1989,[23] localized tetanus was not described specifically except in an experimental study in 1931,[4] in which tetanus remained localized in the majority of

*References 11,13,14,19,23-27,29,30,32,33,37.
†References 6,9,10,15,17,21,23.
‡References 7,8,10,12,17,34.

Table 8-1 | **Summary of All Reports of Tetanus in Cats**

Citation	Age (Years, if Not Noted)	Sex	Breed	Location and Cause of Initial Wound	Location of Initial Tetany	Localized/ Generalized	Antibiotics Used	Other Treatment(s)	Outcome (Time to Full Recovery or Death from Beginning of Clinical Signs)
Fildes et al, 1931	2	M	DSH	Left foreleg (trap injury)	Generalized at presentation	Generalized	—		Euthanized
Bateman, 1931	3 months	MN	Persian cross	Scrotum (castration wound)	Right hindleg	Generalized	—	Surgical debridement and disinfection of wound Antitoxin	Died (day 3)
Hopson, 1932	5 months	M	DSH	Scrotum (castration wound)	Generalized at presentation	Generalized	—		Euthanized
Ludins, 1939	N/A	M	DSH	Left hind foot (trap injury)	Generalized at presentation	Generalized	—	Amputation of foot Antitoxin	Survived (Residual left hind leg stiffness at 4 weeks)
Lettow, 1955	1	N/A	DSH	Right forepaw (trap injury)	Generalized at presentation	Generalized	—		Died (day 9)
Kodituwakku and Wijewanta, 1958	2.5	M	DSH	Right hock (penetrating wound)	Generalized at presentation	Generalized	Penicillin	Antitoxin Chlorpromazine	Died (day 3)
Loeffler et al, 1962	1.5	MN	DSH	Scrotum (castration wound)	Hindlegs	Generalized	Penicillin/ streptomycin	Antitoxin Chlorpromazine	Died (day 6)
Miller, 1963	1	MN	N/A	Left axilla (foreign body)	Left foreleg	Generalized	Penicillin	Wound debridement 4 days before clinical signs of tetanus seen Antitoxin Promazine HCl	Residual left foreleg lameness at 17 days (no further follow up)
Bradney, 1975	4	MN	N/A	Left dorsal carpus (laceration)	Generalized	Generalized	Penicillin G Lincomycin (from day 13)	Wound debridement (8 days before onset of clinical signs and again on day 0 and day 13) Antitoxin Xylazine Pentobarbitone	Clinically normal at 6 weeks
Goetz, 1976	N/A	N/A	N/A	Hind foot (trap injury)	Hindlegs	Generalized	Penicillin G		Died (day 9)
Saranta, 1976	1.5	F	Siamese	Not noted	Generalized at presentation	Generalized	Penicillin G	Antitoxin Xylazine	Clinically normal at 6 weeks
Killingsworth et al, 1977	2	M	DSH	Right hind foot (trap injury) or scrotum (castration wound)	Generalized at presentation	Generalized	Penicillin	Amputation of digits 2 to 5 RHL before onset of clinical signs Antitoxin Diazepam Chlorpromazine Phenobarbitone Methocarbamol	Clinically normal at 13 weeks
Adeyanju, 1985	1	M	DSH	Not found	Hindlegs	Generalized	Penicillin G	Antitoxin Promazine HCl	Died (day 10)
Godwin, 1985	3	M	DSH	Left hock (penetrating wound	Left gastrocnemius	Generalized	Penicillin	Antitoxin Diazepam	Died

Robinson, 1985				Femur (compound fracture)	Affected leg	Generalized	Yes (no further details)	Antitoxin	Survived (no further details)
Baker et al, 1986	8	FN	DSH	Right carpus (trap injury)	Right foreleg	Generalized	Penicillin G	Antitoxin Acepromazine	Clinically normal at 10 weeks
	4 months	F	DLH	Left hindleg (trap injury)	Both hind legs	Generalized	Ampicillin	Wound debridement 5 days before onset clinical signs	Euthanized
Daigo, 1988	1	F	DSH	Not noted	Generalized at presentation	Generalized	Penicillin G Kanamycin	Chlorpromazine	Clinically normal at day 45
Malik et al, 1989	3	M	DSH	Left forepaw (trap injury)	Left foreleg	Localized	Amoxicillin	Wound debridement 20 days before and again 2 days after onset of clinical signs Prednisolone	Euthanized
	11	FN	DSH	Left carpal pad (trauma)	Left foreleg	Localized	Trimethoprim/ sulfadiazine	Wound debridement 1 day before onset of clinical signs Prednisolone Diazepam	Clinically normal at 12 weeks
Touffut et al, 1992	1	F	ESH	Right hindleg (trauma)	Right hindleg	Localized	Amoxicillin	Antitoxin	Clinically normal at 8 weeks
Bieringer, 1994	13	MN	ESH	Abdominal hernia	Generalized at presentation	Generalized	Penicillin	Diazepam	Clinically normal at 4 weeks
	2	F	ESH	Phalanges of right foreleg (chemical burns create ulcers on pads of both forelegs and left hindleg)	Right foreleg	Localized	Penicillin	Diazepam	Clinically normal at 12 weeks
McKee, 1994	4	M	DSH	Left scapular (penetrating wound)	Left foreleg	Localized	Amoxicillin/ clavulanate		Clinically normal at 10 weeks
Seyrek-Intas, 1995	1.5	FN	Turkish	Ovariohysterectomy (left flank incision)	Left hindleg	Generalized		Ketorolac (NSAID) Xylazine Vitamin B_1	Died
	8 months	M	Turkish	Right foreleg (abscessation)	Right foreleg	Generalized	Ampicillin		Died
Lee and Jones, 1996	8 months	FN	Burmese	Ovariohysterectomy (left flank incision)	Epaxial musculature and left hindleg	Localized	Benzyl penicillin then amoxicillin	Antitoxin Diazepam Methocarbamol	Clinically normal at 12 weeks
	9 months	FN	DSH	Ovariohysterectomy (left flank incision)	Epaxial musculature and left hindleg	Localized	Amoxicillin	Diazepam	Spasticity reduced over 6 weeks then lost to follow up
Klaffer and Gutbrod, 1996	Adult	F	Not specified	Abdominal trauma	Generalized at presentation	Generalized	Day 1-2, amoxicillin Day 3-11, clindamycin	Antitoxin Diazepam	Clinically normal at 12 days
	Adult	M	Not specified	Tibial fracture heavily contaminated with soil, repaired with plate 10 days before signs	Generalized at presentation	Generalized	Amoxicillin	Diazepam Flushed wounds Methocarbamol Narcotics	Died day 5
Habibah et al, 1998	11	M	DSH	Right carpus (puncture wound)	Right foreleg	Localized	Penicillin G Metronidazole	Antitoxin Acepromazine	Clinically normal at 3 weeks

Continued

Table 8-1 | **Summary of All Reports of Tetanus in Cats—cont'd**

Citation	Age (Years, if Not Noted)	Sex	Breed	Location and Cause of Initial Wound	Location of Initial Tetany	Localized/ Generalized	Antibiotics Used	Other Treatment(s)	Outcome (Time to Full Recovery or Death from Beginning of Clinical Signs)
Malik et al, 1998	2	MN	DSH	Left hindleg (open tibial fracture)	Unclear, affected limb amputated	Generalized	Amoxicillin/ clavulanate Enrofloxacin Returned to previous antibiotic	Left hindleg amputated 5 days after injury, 2 days before onset clinical signs	Clinically normal at 2 weeks
Polizopoulou et al, 2002	9 months	M	DSH	Right side neck (penetrating wound)	Right foreleg	Localized	Metronidazole	Diazepam	Mild residual lameness at 5 months
	8 months	M	DSH	None found	Both forelimbs	Localized	Metronidazole	Diazepam	Mild stiffness at 2 months
Baral et al, 2002	4	MN	Persian	Tail (trauma)	Left hindleg	Localized	Amoxicillin/ clavulanate Metronidazole	Diazepam	Clinically normal at 4 weeks
Costa et al, 2002	3	MN	DSH	Scrotum (castration wound)	Hindlegs	Generalized	Penicillin G	Antitoxin Diazepam	Euthanized
De Risio and Gelati, 2003	1	FN	DSH	Digits of left foreleg (abrasive trauma)	Left foreleg	Generalized	Amoxicillin/ clavulanate Metronidazole	Antitoxin Diazepam	Clinically normal at 3 weeks
Phillips, 2004	6 months	FN	DSH	Ovariohysterectomy (midline)	Hindlegs	Localized	Penicillin Metronidazole	Antitoxin Diazepam Buprenorphine	Clinically normal at 3 weeks
Tomek et al 2004	3	FN	DSH	Right hindleg (femoral fracture with plate fixation)	Right hindleg	Localized	Penicillin G	Medetomidine Buprenorphine	Clinically normal at 8 weeks
	4	MN	DSH	Right axillary abscess	Right foreleg	Localized	Benzyl penicillin then amoxicillin/ clavulanate	Antitoxin	Clinically normal at 5 weeks
	16	FN	DSH	Right side neck	Generalized?? at presentation	Generalized	Amoxicillin/ clavulanate Metronidazole	Phenobarbitone Acepromazine Pentobarbitone	Clinically normal at 5 weeks

cats. The distribution of localized to generalized cases (15:5) recorded since then is likely an accurate reflection of the relative occurrence of these different syndromes. In other words, localized tetanus probably is three times as common as generalized tetanus in cats. Many cases recorded before 1989 started as a localized phenomenon, before progressing to generalized tetanus, including one case from the pre-antibiotic era.[7]

PATHOGENESIS

Tetanus develops when bacterial spores introduced into a wound are able to germinate as a result of anaerobic conditions. Anaerobic conditions are aided by factors that reduce the local oxidation-reduction potential, such as the presence of a foreign body, tissue necrosis subsequent to trauma, or suppuration. In addition tetanolysin, an exotoxin produced by the vegetative forms of *C. tetani,* is believed to be capable of damaging viable tissue surrounding a wound, which provides further conditions suitable for anaerobic growth.[3]

The typical clinical sign of unyielding rigidity is caused by the centrally acting neurotoxin TeNT, an exotoxin elaborated by the vegetative forms of *C. tetani.*[3] This exotoxin is one of a distinct group of metalloproteases (of which the botulinum neurotoxins are the only other members). The origin of this group has not been traced to any of the known family of enzymes.[39] From its site of production, toxin diffuses through extracellular fluid (ECF) to nerve endings, specifically the presynaptic membrane of cholinergic axon terminals, where it binds to specific receptors.[2,40] Once bound, toxin is internalized into vesicles in the nerve terminal and therefore is no longer accessible for neutralization by antitoxin. Retrograde migration of TeNT along the motor axons towards the ventral roots and spinal cord has been shown to occur at a rate of 85 to 170 mm per day in vitro[41] and 70 to 310 mm per day in vivo.[42] The incubation period therefore varies from 3 to 18 days after an injury and is influenced by the proximity of the injury to the CNS, the degree to which local oxidation-reduction potential favors toxin elaboration, and the numbers of spores/organisms inoculated. To reach its final site of action, TeNT must reach motor neuron cell bodies and adjacent inhibitory interneurons. In this location, TeNT cleaves the vesicle-associated membrane protein (VAMP or synaptobrevin), which inhibits the release of inhibitory neurotransmitters (glycine and γ-aminobutyric acid [GABA]) from interneuron nerve terminals, which thereby causes excessive motor neuronal discharge through disinhibition.[2,41,43] These effects are noted predominantly at the spinal cord; however, the brainstem and autonomic nervous system also can be affected.[2,3]

The reason for cats' innate resistance to tetanus toxin in naturally occurring cases has not been elucidated precisely, but is thought to relate to differences in the binding of TeNT to peripheral and central presynaptic terminals.[2] When tetanus toxin has been administered peripherally in experimental studies, cats are highly resistant to its effects but are extremely sensitive to TeNT when it is injected directly into the spinal cord.[44]

With prompt recognition and appropriate treatment, the disease can be restricted to its localized form. Localized tetanus, however, may progress to generalized tetanus if treatment is delayed or inappropriate, because more toxin will be produced by vegetative forms of *C. tetani* in the tissues.

CLINICAL SIGNS

In many reported cases, clinical signs have started as tetanic spasm of a localized group of muscles in close proximity to a wound. In the early stages, tetany may manifest as an altered gait, but typically this progresses rapidly to rigidity of the affected limb or muscle group. Intermittent spasms may be superimposed on the tonic rigidity. Pain perception remains intact and myotatic reflexes are normal to accentuated but may be difficult to elicit as a result of the rigidity.[17,23] In the thoracic limb, the elbow usually is extended rigidly with the carpus either extended or flexed (Figure 8-1). Pelvic limbs are held with the stifle and hock extended (Figure 8-2). These signs are strongly suggestive, if not pathognomonic, for localized tetanus. Localized tetanus of epaxial musculature also has been reported, invariably subsequent to ovariohysterectomy.[8,36] Progression from localized to generalized tetanus can occur over a time frame of between 12 hours[7] and 7 days[21,23] when appropriate medical interventions are not instituted. Typically

Figure 8-1. Localized tetanus that affects the left thoracic limb. Note the elbow is extended rigidly, whereas the carpus is flexed.

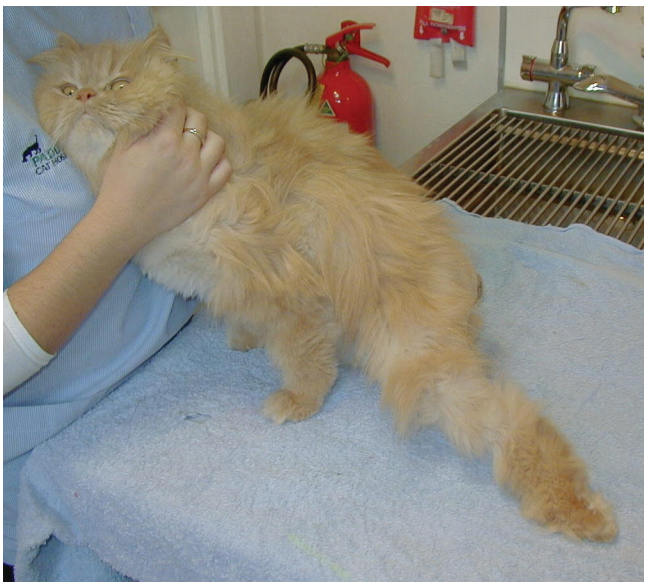

Figure 8-2. Localized tetanus involving the left pelvic limb. The toes are extended such that the cat cannot place the palmar surface of its paw on the benchtop.

this progression takes 2 days.[6,19] Progression usually is to the contralateral extremity; however, the signs of tetanus may extend from a forelimb to the ipsilateral hindlimb before becoming generalized.[27]

Progression to generalized tetanus results in rigidity of all limbs and the epaxial musculature, resulting in opisthotonos (Figure 8-3). In addition, characteristic facial signs may be present, including erect ears, trismus (lockjaw), reduced palpebral fissures, protrusion of the nictitating membranes (especially after eliciting a blink reflex), and drawn-back lips (the "sardonic smile" of tetanus, or risus sardonicus) (Figure 8-4). This combination of signs is pathognomonic for generalized tetanus. Cats may have sialosis because of an inability to swallow and increased sympathetic activity. Elevations in respiratory and heart rates also occur. Patients often are hypersensitive to auditory or tactile stimuli and may respond by tonic contractions. Cats remain conscious, appear to be in pain, and may vocalize.[6] Dysuria and urinary retention have been reported on several occasions[7,17,21,34,35] in addition to difficulty with prehension and swallowing, although cats may remain interested in eating.[9,17,31] Progression of signs results ultimately in death, usually from respiratory compromise because of involvement of the intercostal muscles and diaphragm, spasms of the larynx, increased airway secretions, and central respiratory arrest from medullary intoxication or anoxia.

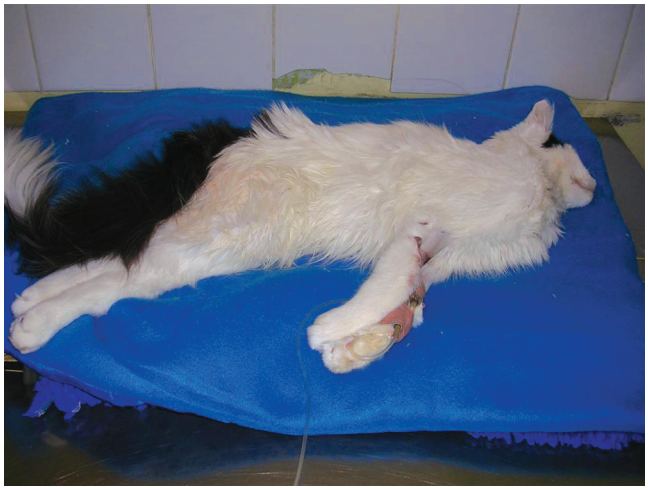

Figure 8-3. Cat with generalized tetanus and large wound over the lateral aspect of the left hindlimb. Note particularly the rigid extension of hindlimbs and typical facial expression (partially obscured).

Figure 8-4. Facial features of cat with generalized tetanus. Note the erect ears, reduced palpebral fissures, and drawn back lips (risus sardonicus).

In a number of cases, wounds either have not been found[18,32] or have appeared to heal uneventfully[20,27,28,33,36] by the time sufficient toxin had reached the spinal cord to cause clinical signs. Large volumes of bacteria are not required to produce sufficient toxin to cause the clinical signs of tetanus. *C. tetani* is thought to produce relatively large volumes of toxin during the stationary phase of growth, which then is released during cell autolysis, rather than during the exponential phase of growth.[40]

In approximately one third of generalized tetanus cases, the patient was not presented until generalized signs were present. In these cases, cats either progressed from unrecognized localized tetanus or developed generalized signs from the outset.

DIFFERENTIAL DIAGNOSIS

Tetanic spasm of a localized muscle group is virtually pathognomonic for localized tetanus, especially when signs follow the history of a necrotic lesion in a compatible anatomical site. Much less likely differential diagnoses include localized meningitis, neuritis or myelitis of peripheral nerves or nerve roots resulting from toxoplasmosis, feline infectious peritonitis, neoplasia, or unknown causes.

In many cases, generalized tetanus is recognized as a progression from local tetanus and thus precludes the possibility of alternative diagnoses. For cats that present with generalized tetany, differential diagnoses that should be considered include hypocalcemic tetany, decerebrate rigidity, subarachnoid hemorrhage or cyst, and strychnine poisoning. These should be ruled out by history, serum biochemistry, radiography, and/or response to therapy.

DIAGNOSIS

In most cases, a strong tentative diagnosis can be made from clinical signs and history. Extreme spasticity localized to one limb subsequent to penetrating trauma is sufficiently distinctive to diagnose localized tetanus confidently.* Most cases of generalized tetanus are recognized after initial localized tetany, whereas the clinical stigmata of trismus, risus sardonicus, and nictitans prolapse are typical of this condition.

Hematology may or may not reflect localized infection or concurrent stress. Serum biochemistry usually is unremarkable but elevations in creatine kinase[28,34,35] or aspartate aminotransferase would not be surprising. Radiography generally is noncontributory, although it should be noted that megaesophagus and hiatal hernia have been reported in dogs with tetanus.[45-47]

* References 23,24,26,28,30,32,33.

Table 8-2 | **Diagnostic Criteria for Localized Tetanus**

An alert, healthy patient
Spasticity of a limb or group of muscles innervated by the same or adjacent spinal nerve(s)
Physical or historical evidence of an infected focus nearby, suitable for the proliferation of *C. tetani* and the elaboration of tetanus toxin
The wound should be close to or distal to the spastic muscle groups
Slow but complete resolution, with muscular rigidity subsiding over many weeks to months
The presence of clostridial organisms in Gram-stained smears, or isolation by culture of *C. tetani* from the contaminated wound
Characteristic EMG findings under general anesthesia
Elevated serum tetanus antibody concentrations

Cerebrospinal fluid analyses and muscle biopsies are unremarkable.

Definitive diagnosis of tetanus can be confirmed by isolation of *C. tetani* from an infected focus, although neurological signs may not occur until after the initiating wounds have healed.[20,21,23,28] Culturing anaerobic bacteria can be challenging; therefore failure to culture *C. tetani* does not exclude this diagnosis. Determination of serum tetanus antibody titers may be useful[21] but these are of very limited availability. Needle electromyography (EMG) typically demonstrates persistent motor unit activity that persists under general anesthesia[28,32,37] but is not readily available in general practice. Diagnostic criteria for local tetanus have been developed for human and veterinary medicine[23,28,33,48] and are summarized in Table 8-2.

TREATMENT

The prognosis for localized tetanus is uniformly good, and approximately two thirds of cats reported with generalized tetanus over the last 40 years have survived. Clinical signs typically resolve completely within 2 to 3 months[17,21,23,26,28] but the recovery can be as short as 2 to 3 weeks.[29-31,33] Counterintuitively, recovery can be faster in generalized than in localized cases.

Localized tetanus can become generalized in cases of inadequate wound management, inappropriate antibiosis, or concurrent use of corticosteroids. A case reported from the pre-antibiotic era noted a cat that progressed from localized to generalized tetanus,[7] as did a cat in a contemporary paper for which an inappropriate antibiotic (a fluoroquinolone) was used.[31] Antibiotics used for treating tetanus patients must have the following features: activity against all strains of *C. tetani*, bactericidal, available in intravenous formulations (for treatment of generalized cases), devoid of significant toxicity, and effective at penetrating poorly perfused necrotic foci. Crystalline benzyl penicillin and metronidazole probably are the agents of choice. Although metronidazole has been shown to be slightly superior to benzyl penicillins in human studies,[49] high doses themselves can cause neurological dysfunction in cats.[50] Therefore, the authors currently recommend either high-dose (30 mg/kg q6h IV) benzyl penicillin therapy or combination therapy of benzyl penicillin (dose as above) with metronidazole (10 mg/kg q12h IV). Ampicillin (20 to 30 mg/kg q8h IV) does not appear to have been assessed critically but most likely has the required features and potentially could be used. Intravenous antibiotics generally are required only for the first 3 to 5 days of therapy. The localized form of the disease can be managed for the most part with oral antibiotics such as amoxicillin (20 mg/kg q12h), amoxicillin with clavulanic acid (at least 15 mg/kg q24h), or metronidazole (no greater than 25 mg/kg q24h). A treatment course of 10 to 14 days is likely to be adequate, although antibiotics must be continued until any discernable wound has healed completely.

Wound debridement or amputation in the case of devitalized limbs is an important part of therapy for any disease involving *Clostridia* spp. In the reported cases of feline tetanus, several cats had appropriate wound debridement at the time of presentation yet manifested clinical signs of tetanus within 2 to 7 days, which suggests that liberation and centripetal migration of tetanus toxin already had commenced.[13,14,17,21,23]

In addition to wound debridement and aggressive antimicrobial therapy, other potential treatments include tetanus antitoxin and muscle relaxants. Tetanus antitoxin cannot dislodge TeNT after its entry into peripheral nerves. Therefore its main purpose would be to neutralize toxin outside the nervous system, either near the wound or in the systemic circulation.[28,30] This is unlikely to be necessary if signs are chronic, localized, and/or nonprogressive. Of the 14 cats reported with localized tetanus since its recognition, 13 survived (one case[23] was euthanized because the condition was not recognized). Only five of these cats received antitoxin.[24,28,30,36,37] The use of antitoxin did not appear to have made a difference to the disease course, although the potential neutralization of accessible toxin may have helped avoid progression to generalized tetanus in these cases.

The decision to use or not use tetanus antitoxin must be made on a case-by-case basis. For generalized tetanus to occur, sufficient TeNT must be present, some of which may remain in ECF or the systemic circulation even after wound debridement. The neutralization of this portion of TeNT is the rationale for antitoxin therapy. Use of tetanus antitoxin of equine or human origin may result in anaphylaxis, and this risk must be assessed in light of the severity of clinical signs versus the benefit of neutralizing unbound toxin. Currently 16 reports exist of administration of antitoxin of equine origin to cats. Only one of these patients appears to have had an anaphylactic reaction.[19] Antitoxin of human origin has been administered to one cat, also with no adverse effects.[35] The risk of anaphylaxis can be reduced further by dilution of the antitoxin in 20 mL of saline, administration of the product slowly, and premedication of the cat with 0.2 to 0.3 mL of 1:1000 epinephrine subcutaneously a few minutes before antitoxin administration.

The main benefit of muscle relaxants and sedative agents is to reduce discomfort and pain during the prolonged recovery period.[28] Both acepromazine and benzodiazepines (e.g., diazepam or midazolam) may be useful in this setting, and these agents used concurrently may produce the optimal combination of sedation and muscle relaxation in cases of generalized tetanus. Diazepam has been used most often and sometimes achieves noticeable relief[23] but in other cases appears to be of no benefit.[28]

Cats with severe, generalized tetanus are challenging and demanding to treat. In addition to prevention of painful spasms with sedatives such as acepromazine and relief of tonic rigidity using benzodiazepines or methocarbamol, these cats require symptomatic and supportive therapy. Placing an indwelling IV catheter facilitates administration of IV antibacterial agents and other medications, in addition to providing ongoing

maintenance fluid requirements. The eyes should be lubricated regularly with a suitable ointment. Animals ideally should be nursed in sternal recumbency or turned regularly; however, sometimes they seem much more comfortable in a particular posture. Midazolam (0.3 mg/kg IV or SQ) should be administered before manipulations such as turning or bandage changes. No food should be given orally in the first 3 to 5 days because of spasm of pharyngeal muscles and difficulty swallowing, with the attendant risk of aspiration. After that time, provided obvious clinical improvement occurs, nutritional support can be provided by syringe feeding. Alternatively, an esophagostomy or gastrostomy tube can be placed for convalescence (see Chapter 16). Most cats are capable of swallowing and prehension 7 to 14 days after starting therapy.

CONCLUSION

Tetanus is a rare diagnosis in cats because of this species' innate resistance to tetanus toxin. Most cases start as localized tetanus. Avoiding progression to generalized tetanus depends on early diagnosis, appropriate wound management, and antibiosis. Because a definitive diagnosis is difficult to achieve, recognition of the typical patterns of disease is important to ensure appropriate management and to prevent progression to generalized tetanus. Cases that present with generalized signs need IV fluid therapy, IV antibiotics, antispasticity therapy, and, potentially, tetanus antitoxin to effect a favorable outcome. Even though these cases are challenging to treat, the generally favorable prognosis makes the effort gratifying for patient, owner, and veterinarian.

ACKNOWLEDGMENT

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Chapter 9

Odontoclastic Resorptive Lesions

Kenneth F. Lyon

The most common disease of the domestic cat is a resorptive lesion of the teeth. The preferred term, which reflects the process of tooth destruction, is feline odontoclastic resorptive lesions (FORLs).[1] FORLs have been called neck lesions, cervical neck lesions, cervical line erosions, cervical line lesions, feline caries, feline cavities, feline dental resorptive lesions, feline osteoclastic resorptive lesions, and subgingival resorptive lesions.[2-13] Resorptive lesions often are seen first subgingivally at the neck of the tooth (Figures 9-1 and 9-2), which is why they were termed neck lesions initially. This confusing term should not be used to describe resorptive lesions.

The resorptive lesions frequently are covered with dental calculus and may be difficult to diagnose on physical examination of the oral cavity (Figures 9-3 and 9-4). Gingival tissues also tend to migrate into the defects and form hyperplastic tissue, which further obstructs the diagnosis of the lesions. Because dentin tubules are exposed, resorptive lesions are painful when probed, and many cats have a painful mouth with some reluctance to chew. This destruction of the tooth and periodontal attachment eventually leads to tooth loss.

Resorptive lesions in cats were reported initially in the human dental literature in a study conducted in the 1920s and published by Hopewell-Smith[14-15] (Figure 9-5). The Schild excavation unearthed 1871 feline bones from at least 181 cats from the town market of medieval (thirteenth and fourteenth centuries) Schleswig, Germany.[16] Resorptive lesions were present in teeth in three mandibles and a maxillary fourth premolar (Figure 9-6). This evaluation established the presence of resorptive lesions in cats living 800 years ago. Previous evaluations of skull collections found no lesions.[17-18]

Incidence studies reveal that FORLs occur in 29 to 67 per cent of domestic cats.[1,19,20] They have been reported in captive felids[22-24] and in dogs.[25-29] The prevalence has increased in domestic cats since the 1960s. A higher incidence is seen with increasing age of cats. Some studies have found an increased incidence of resorptive lesions in cats with periodontal disease. However, although cats with gingivostomatitis may have resorptive lesions, most cats with gingivostomatitis are not affected.

FORLs are considered to be progressive defects of the calcified tooth substance of permanent teeth, which results from the destructive activity of odontoclasts on the root cementum. This often is called external resorption because the destruction is occurring on the external tooth surface. Internal resorption refers to the odontoclastic activity that occurs in dentin adjacent to the pulp canal.[30-31]

The roots of permanent teeth normally do not undergo resorption. The cementum and periodontal ligaments are organic, uncalcified components. This covering of the external surface of tooth roots appears to have a resorption-inhibiting characteristic. If these protective layers are altered, odontoclasts may be attracted and attach to the exposed calcified tissue of the tooth root.[1,32]

Two conditions must be present for local root resorption.[1] First, the protective covering of the root must be missing or altered. Second, a stimulus for the resorbing cells must be present. The roots of permanent teeth are resistant to resorption on external surfaces and internally on the pulp tissue interface. On the external root surface, cementoblasts and cementoid form the outermost layer of root cementum. On its internal surface, a layer of odontoblasts and predentin lines the pulp canal and contacts the pulp tissues.

Cementoblasts and cementoid, in addition to odontoblasts and predentin, are uncalcified organic root components that may have resorption-inhibiting characteristics. Odontoclasts may be attracted only to, or can attach only to, mineralized tissue. If mineralized tissue is not present, the odontoclast will not be attracted to the root surface. Theories suggest that removal or calcification of the organic matrix of the root covering makes it possible for odontoclasts to recognize the mineral component.[32-34] Periodontal disease (plaque bacteria and their toxins) and other possible causes of local

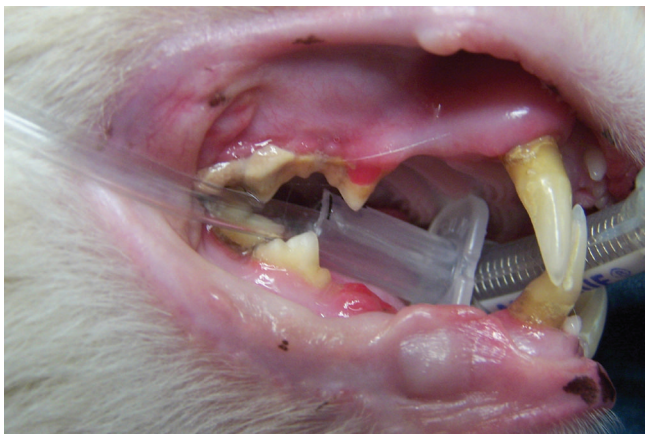

Figure 9-1. Resorptive lesion on the right maxillary third premolar (tooth 107).

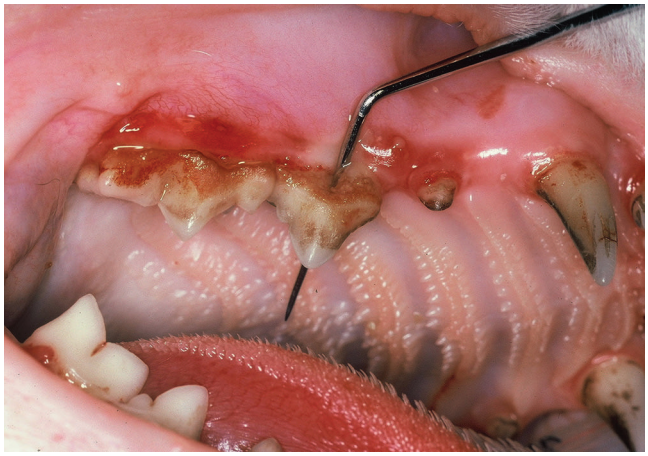

Figure 9-2. Probing the furcation of the right maxillary third premolar (tooth 107) for resorptive lesion.

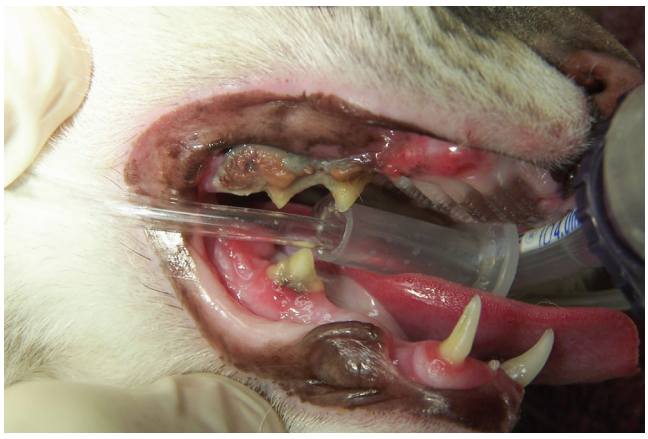

Figure 9-3. Heavy dental calculus covering resorptive lesions in the right maxillary third and fourth premolars (teeth 107, 108).

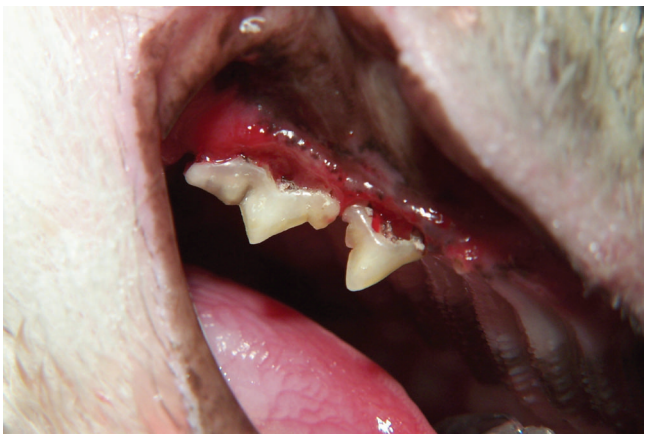

Figure 9-4. Resorptive lesions (from Figure 9-3) in the right maxillary third and fourth premolars (teeth 107, 108) become obvious after ultrasonic scaling.

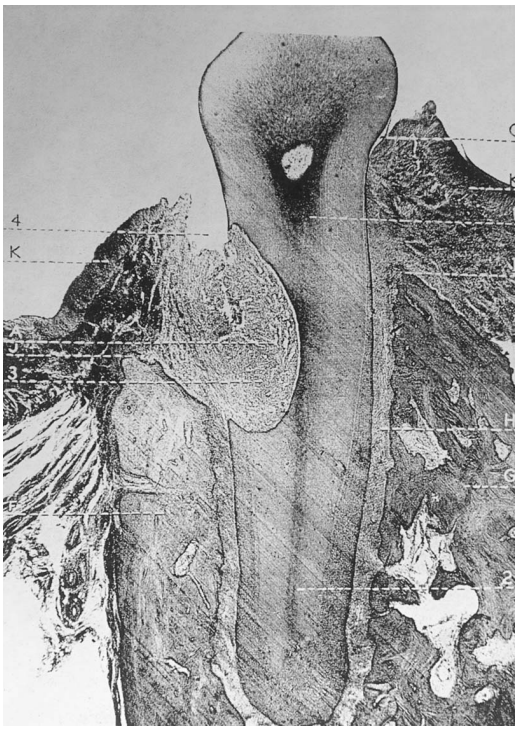

Figure 9-5. Resorptive lesions of cat teeth from the 1920s from the Hopewell-Smith publication. (From Reiter AM: Feline "odontolysis" in the 1920s: the forgotten histopathological study of feline odontoclastic resorptive lesions (FORL). J Vet Dent 15:35-41, 1998, with permission.)

inflammatory activity then may provide the inflammatory stimulus (cytokines) for resorption of alveolar bone and teeth.[35-37]

The pathophysiology of resorptive lesions was described in the early 1990s and is related to cytokine release that stimulates the clastic activity.[38,39] Cytokine release occurs in inflammatory reactions and can be stimulated by local immune responses.[40,41] Interleukin expression is higher in teeth with resorptive lesions compared with normal teeth. Etiological theories include occlusal overload, which causes microfracture of cementum that leads to the inflammatory resorptive events.[35,42] The etiology of resorptive lesions in cats is still under investigation. Recent studies suggest a dietary influence related to calcium regulating hormones and particularly related to the excessive dietary intake of vitamin D, which is associated with root surface changes leading to resorption.[32-34]

Figure 9-6. Resorptive lesion in fourteenth century cat mandibular molar (tooth 309). (From Berger M, Stich H, Hüster H, et al: Feline dental resorptive lesions in the 13th and 14th centuries. J Vet Dent 21(4):206-213, 2004, with permission.)

ETIOLOGY

Determining the cause of FORLs in cats is a continuing process. Diet frequently has been discussed as a contributing cause of resorptive lesions in cats.[43-45] Evidence suggests that increased dietary intake of vitamin D is associated with a higher incidence of resorptive lesions in cat teeth, but the causative factors leading to the development of resorptive lesions are still unknown.[33,34]

DIETARY FACTORS

Cats with FORLs have significantly higher serum 25-hydroxyvitamin D (25OHD) concentrations than cats without FORLs.[32,38] Cats with FORLs are significantly more likely to have detectable calcitonin (CT) in their serum. Cats are not able to synthesize vitamin D_3 in the skin sufficiently, and a direct linear relationship exists between serum concentration of 25OHD and dietary intake of vitamin D. In the results of one study,[32-34] concentrations of 25OHD indicated that cats with resorptive lesions had ingested higher amounts of vitamin D or vitamin D metabolites, compared with cats without resorptive lesions.[46-50] Many commercially available cat foods contain excess concentrations of vitamin D.

Serum concentrations of calciotropic hormones never have been evaluated in cats with resorptive lesions. No significant differences existed in serum concentrations of parathyroid hormone (PTH), parathyroid hormone–related peptides (PTHrP), and tetraiodothyronine between cats with and without resorptive lesions.[32-34] 25OHD serum concentrations, however, were significantly higher in cats with resorptive lesions (mean 112.4 nmol/L) as compared with cats without resorptive lesions (mean 89.8 nmol/L).[32-34] CT was detected significantly more frequently in sera of cats with resorptive lesions than in cats without resorptive lesions, which may reflect the body's response to increased clastic cell action.

Classic clinical and laboratory signs of vitamin D toxicosis include vomiting, increased serum 25OHD concentrations, hypercalcemia, hyperphosphatemia, azotemia (increased blood urea nitrogen and creatinine), and decreased specific gravity (see Chapter 17).[51-54] In this study,[34] cats with FORLs vomited significantly more often (mean 2.2 times per month) than cats without FORLs (mean 0.9 times per month). Mean 25OHD serum concentration was significantly higher in cats with FORLs (112.4 nmol/L), compared with cats without FORLs (89.9 nmol/L). The risk of FORLs increased by 2 per cent for each nmol/L elevation of 25OHD. Except for two intact males, all other cats in the study were neutered. Routine neutering may result in deficient estrogen production that could alleviate increased vitamin D activity. Calcitonin was detected significantly more often in sera of cats with FORLs (28.8 per cent), compared with cats without FORLs (13.3 per cent).[32-34]

Mean serum concentration of blood urea nitrogen was significantly higher in cats with FORLs (26 mg/dL), compared with cats without FORLs (22.43 mg/dL). Serum concentration of creatinine in cats with FORLs was higher (1.7 mg/dL) than in cats without FORLs (1.56 mg/dL), although this difference was not significant. Urine specific gravity was significantly lower in cats with FORLs (mean 1.0263), compared with cats without FORLs (mean 1.0366). For each unit decrease in urine specific gravity, the risk of resorptive lesions increased by 31 per cent. Although the group mean values of renal parameters remained within the reference range, the results suggest an impairment of renal function in cats with resorptive lesions.[32-34]

Although higher serum 25OHD concentrations were noted in cats with resorptive lesions, homeostatic regulation of serum total and ionized calcium was maintained within reference ranges, presumably through an enhanced metabolism of vitamin D or by the effective regulation of other hormones responsible for calcium homeostasis.[34]

In numerous experimental studies, excess administration of vitamin D or vitamin D metabolites has caused dental and periodontal changes that resemble feline odontoclastic resorptive lesions.[31,55,56] In this study,[34] cats with resorptive lesions had significantly higher serum 25OHD concentrations compared with cats without resorptive lesions, which indicates that increased vitamin D intake may play a role in the development of resorptive lesions. Chronic intake of increased concentrations of vitamin D may alter the resorption-inhibiting characteristics of the periodontal ligament and root surface, which invites inflammation caused by periodontal disease and other possible causes of inflammatory activity to attack alveolar bone and the teeth by stimulated clastic cells.[34] Increased vitamin D activity in cats with resorptive lesions may be the key to solving an enigma in veterinary dentistry.

Excess vitamin D intake may alter the resorption-inhibiting characteristics of the root surface covering in cats. Fusion of the root to the alveolar bone or ankylosis results from calcification of the periodontal ligament, hypercementosis, and hyperosteoidosis. The ankylosed tooth then becomes involved in the process of normal bone remodeling, which leads to the gradual resorption of the roots and replacement by bone. This is known as replacement resorption. If granulation tissue at the gingival margin migrates into the resorptive lesion, an

inflammatory reaction contributes to the resorptive lesion (inflammatory resorption). Chronic excessive dietary intake of vitamin D may play a role in idiopathic hypercalcemia and renal disease in older cats (see Chapter 17).

PERIODONTAL DISEASE

Plaque bacteria obviously are the cause of chronic periodontal disease.[5,57-62] The focus in understanding recurrent oral disease is on determination of the impact of these bacteria on the immune response and the interaction of the host's defense mechanisms. The response of each site to a specific plaque composition is regulated by the individual immune system. Periodontal disease results from an imbalance between the host and the local microbial flora. The imbalance may occur when the quantity or quality of bacteria changes, or when the animal's immune response is altered or affected by environmental factors. A good immune response results in no evidence of progressive disease despite the presence of calculus and plaque. A patient with an impaired immune status and less extensive plaque may have generalized or localized evidence of disease.

Inflammation of the periodontium leads to the release of bacterial byproducts such as lipopolysaccharides and inflammatory mediators, especially cytokines.[63,64] Epithelial, endothelial, and inflammatory cells secrete cytokines. Inflammatory cells often are found associated with resorptive lesions, although no significant correlation exists between resorptive lesions and periodontitis. The inflammation associated with resorptive lesions more likely is a secondary reaction related to the plaque accumulation that occurs at the site of the resorptive lesion.[60,62]

Evidence also exists that periapical inflammation can lead to a breakdown in periodontal ligament fibers and resorption of the root apex and bone. The stimulus for osteoclastic activity affecting the root surface and alveolar bone appears to be a combination of direct influence of bacteria and their toxins and an indirect influence of the osteoclast in response to inflammatory changes.[65-69]

NONINFLAMMATORY REPLACEMENT RESORPTION

A study by Gorrel and Larsson was designed to increase the understanding of the factors initiating feline odontoclastic resorptive lesions.[70] Fifty-six teeth (clinically and radiographically unaffected by FORLs) were harvested. Of these, 43 were from cats that had FORLs in other teeth (group A), and 13 were from cats with no clinical or radiographical evidence of FORLs in any teeth (group B). Twenty-six teeth in group A and one tooth in group B showed histological evidence of external root resorption (surface resorption and replacement resorption resulting in ankylosis). Some teeth in group B showed healed cementum resorption.

Previous assumptions were that FORLs were similar to lesions associated with peripheral inflammatory root resorption and were associated with periodontal disease.[70] These histological findings suggest instead that FORL is a noninflammatory replacement resorption that results in ankylosis. The periodontal ligament of resorbing teeth lacked normal fibrous architecture but was not inflamed.[70] Resorption was not identified in cervical cementum. However, the histological appearance of the cervical cementum differed between the two groups. Several etiopathogenetic explanatory models, which arise from these observations, have been discussed.[70]

TRAUMA OF OCCLUSION

Trauma of occlusion, which involves the normal chewing mechanisms, can place excessive forces on the tooth crown. These forces may be transferred apically to the root cementum surface and begin the process of replacement resorption. The traumatic forces cause tears in the periodontal ligament. In the process of attempting to repair these lesions, resorption is stimulated. The initial injury occurs when the periodontal ligament is separated from its attachment to the root surface. When wound healing occurs, the damaged tissue is removed by macrophage and osteoclast activity. Often, cementum on the root surface and alveolar bone of the socket are removed. Competitive wound healing occurs between the cells destined to form bone and the cells that form periodontal ligament fibers and cementum. This results in ankylosis because the alveolar bone cells dominate the healing process. Ankylosis then can lead to further resorption processes.

Occlusal stresses also can contribute to the process of abfraction.[42,71,72] Repetitive tensile and compressive forces caused by tooth flexure during chewing may disrupt the bonds between enamel rods, which results in abfraction of enamel and exposure of the underlying dentin. This exposure of dentin stimulates the movement of odontoclasts into the site, which results in resorption. Evidence suggests that feline enamel is thin and the microhardness of enamel and dentin in the species is low.[73-75]

FURCATION CANALS

Lateral and accessory canals are common in cats and extend from the endodontic system, root canal, and pulp chamber of the crown.[76-79] Although these canals have been seen in feline premolars and molars, they have not been documented in the canine teeth of cats.[80] The intimate anatomical relationship between the pulp and periodontal tissue through the endodontic system, as documented in human beings, makes interaction between both tissue areas possible. The implication is that an infectious or inflammatory process can extend between the pulp and periodontal tissues.

Furcation canals, which connect the pulp chamber with the periodontal ligament, have been described in cats (Figures 9-7 and 9-8). When a pulp injury occurs, resorption of dental tissues and alveolar bone takes place in the furcation area when furcation canals are present. Furcation morphology was evaluated in 103 mature maxillary fourth premolar and mandibular molar teeth of cats. Patent furcation canals were observed in 27 per cent of permanent maxillary fourth premolars and mandibular molars. The presence of these furcation canals could be a factor in the etiological pathogenesis of FORLs, in addition to a characteristic to be considered in the diagnosis, prognosis, and treatment of feline teeth. These furcation areas are prone to resorption when the dentin is exposed and not protected by cementum. Gaps in the cementoenamel junction also may result in exposed dentin, which can stimulate resorptive processes and lead to FORLs.

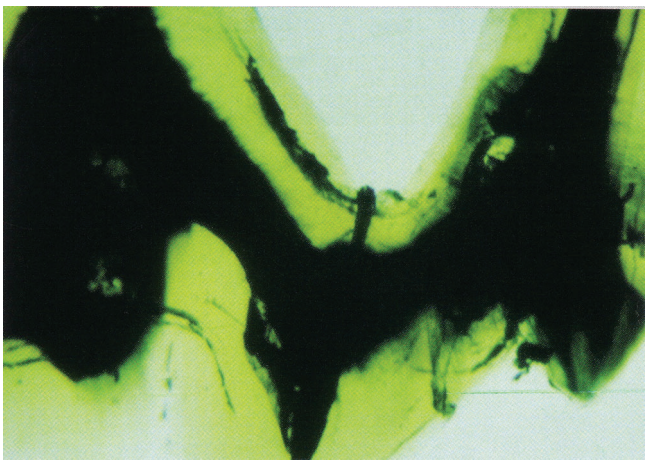

Figure 9-7. Furcation canal of a right maxillary fourth premolar (tooth 108). (From Negro VB, Hernandez SZ, Maresca BM, et al: Furcation canals of the maxillary fourth premolar and the mandibular first molar teeth in cats. J Vet Dent 21:10-14, 2004, with permission.)

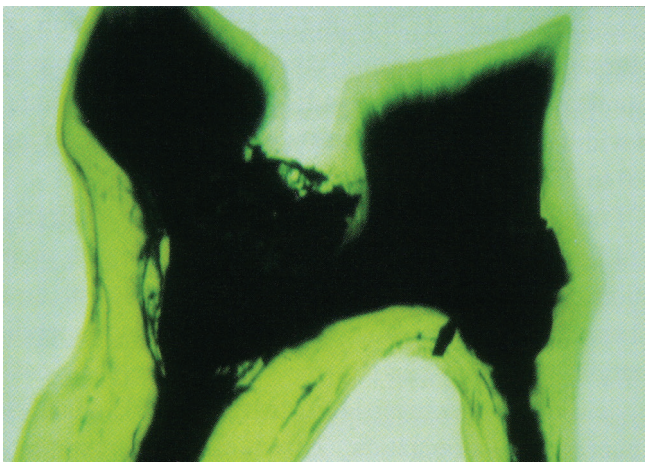

Figure 9-8. Furcation canal of a left mandibular molar (tooth 309). (From Negro VB, Hernandez SZ, Maresca BM, et al: Furcation canals of the maxillary fourth premolar and the mandibular first molar teeth in cats. J Vet Dent 21:10-14, 2004, with permission.)

VIRAL INFECTIONS

Systemic immunosuppressive diseases stimulated by viral infections may aggravate resorption processes, but their ability to initiate resorptive lesions is unlikely. Few cats with resorptive lesions are infected with feline immunodeficiency virus or feline leukemia virus. No evidence exists that these viruses contribute to the development of FORLs. Because viral infections can stimulate oral disease and lead to chronicity, immunosuppression has been mentioned as a possible etiology of resorptive lesions.[81] Calicivirus has been mentioned as a factor in the development of FORLs related to the oral manifestations of calicivirus infection such as gingivostomatitis (see Chapters 1 and 38). However, studies have shown that only a small number of cats with resorptive lesions have chronic gingivostomatitis.[19,82,83]

ENDOCRINE FACTORS

Root resorption has not been seen with primary hyperparathyroidism or renal secondary hyperparathyroidism.[84-88] Tooth roots appear to be resistant to resorption even when significant bone resorption is associated with systemic disease. Estrogens are produced primarily in the ovaries and in small amounts in the testicles and adrenal cortex. Routine neutering of domestic cats has not been associated with the development of resorptive lesions.[1]

PREVALENCE

An increased number of resorptive lesions in cats have been reported since the 1960s. The frequency of feline resorptive lesions is reported to be as high as 75 per cent depending on the cat populations that are evaluated.[1,89] Many of these studies do not include intraoral dental radiographs, and prevalence is based on clinical examination and often without probing for lesions. The likely underestimation of resorptive lesions in some studies may be related to the lack of dental radiographs. Statistically supported information shows that cats younger than 2 years rarely have resorptive lesions and that prevalence of lesions is increasing as cats age.[5,21,90] The number of teeth involved increases as the cat gets older. Neutering, gender, and age at neutering do not appear to affect prevalence of resorptive lesions. Two studies showed that female cats were affected more commonly with resorptive lesions, and one study showed an increase in resorptive lesions in male cats.[36,90,91] Resorptive lesions may occur more commonly in purebred cats, although insufficient data support a breed predisposition. Resorptive lesions are reported to occur more often on the buccal surfaces of premolar and molar teeth and less commonly on incisor and canine teeth of cats. The teeth affected most commonly are the mandibular third premolar and molar and the maxillary third and fourth premolars.

CLASSIFICATION OF FELINE RESORPTIVE ODONTOCLASTIC LESIONS

Resorptive lesions in cats have been classified radiographically and clinically into five stages. Stage 1 lesions extend into cementum only (Figure 9-9). They are not sensitive because they do not enter the dentin. Stage 2 lesions progress through the cementum into crown or root dentin and become painful because dentin tubules are exposed (Figure 9-10). Hyperplastic gingiva and inflammatory granulation tissue often appear to be covering these lesions. Stage 3 lesions advance into the pulp tissues of the crown or root, are painful, and bleed when probed (Figure 9-11). The damaged crown often fractures because of the destroyed root structure. Stage 4 lesions have extensive tooth damage, and ankylosis of roots to the alveolar bone is common (Figure 9-12). These teeth are prone to fracture. Stage 5a lesions often have no crown with only root remnants remaining (Figure 9-13), and in Stage 5b lesions, the crown may be present with extensive root replacement resorption[1,92] (Figure 9-14).

Other classification systems include a Type A through F classification. Type A and B are crown resorptive lesions. Types C and D are resorptive lesions at the cementoenamel junction, and types E and F are resorptive lesions of the root. Types A, C,

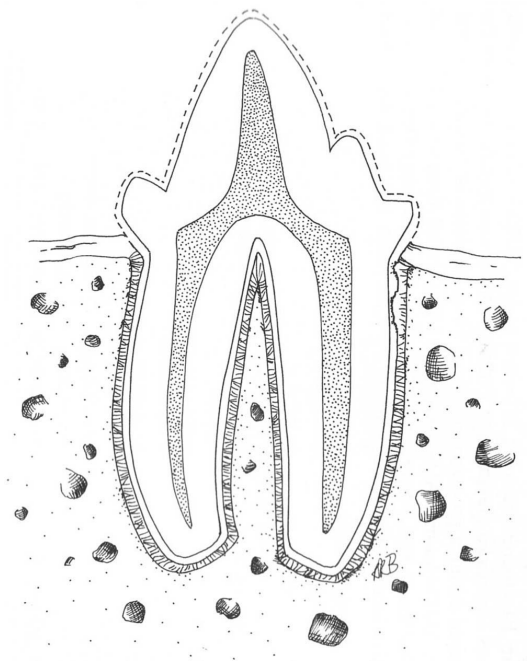

Figure 9-9. Stage 1 feline odontoclastic resorptive lesion affecting only the root cementum. (Illustration by Rebecca Rae Bradford. From Reiter AM, Mendoza K. Feline odontoclastic resorptive lesions. An unsolved enigma in veterinary dentistry. Vet Clin North Am Small Anim Pract 32:791-837, 2002, with permission.)

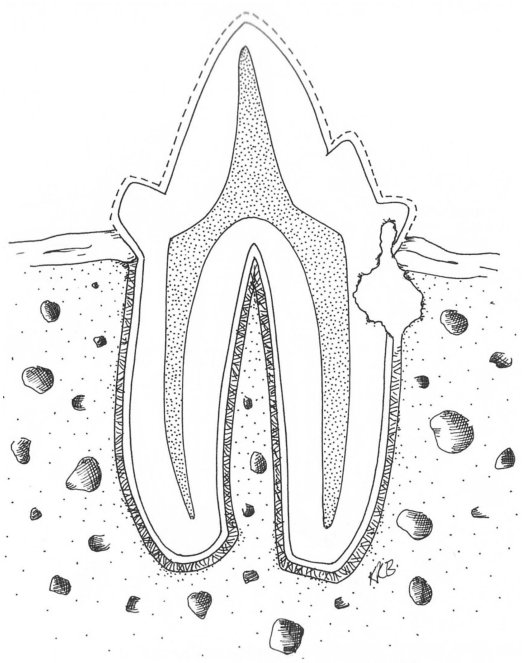

Figure 9-10. Stage 2 feline odontoclastic resorptive lesion progressing into the dentin. (Illustration by Rebecca Rae Bradford. From Reiter AM, Mendoza K: Feline odontoclastic resorptive lesions. An unsolved enigma in veterinary dentistry. Vet Clin North Am Small Anim Pract 32:791-837, 2002, with permission.)

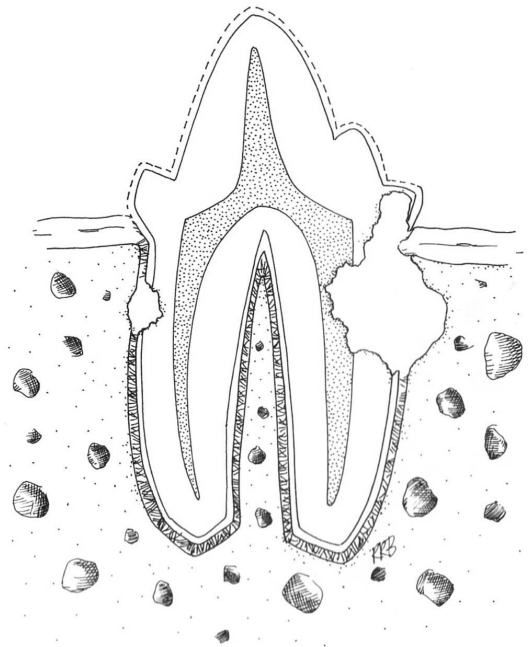

Figure 9-11. Stage 3 feline odontoclastic resorptive lesion entering the pulp cavity. (Illustration by Rebecca Rae Bradford. From Reiter AM, Mendoza K: Feline odontoclastic resorptive lesions. An unsolved enigma in veterinary dentistry. Vet Clin North Am Small Anim Pract 32:791-837, 2002, with permission.)

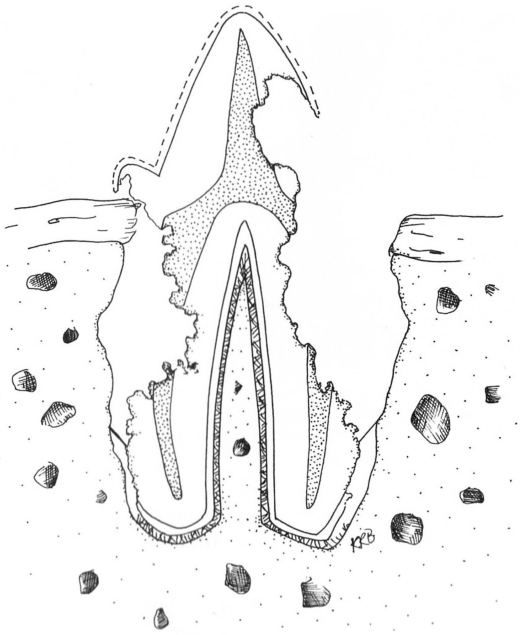

Figure 9-12. Stage 4 feline odontoclastic resorptive lesion with extensive structural damage and dentoalveolar ankylosis. (Illustration by Rebecca Rae Bradford. From Reiter AM, Mendoza K: Feline odontoclastic resorptive lesions. An unsolved enigma in veterinary dentistry. Vet Clin North Am Small Anim Pract 32:791-837, 2002, with permission.)

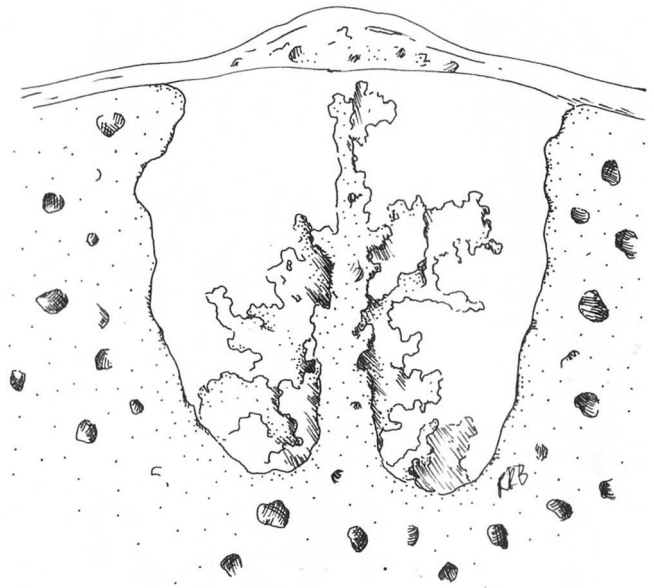

Figure 9-13. Stage 5a feline odontoclastic resorptive lesion with an absent crown and retained root structure. (Illustration by Rebecca Rae Bradford. From Reiter AM, Mendoza K: Feline odontoclastic resorptive lesions. An unsolved enigma in veterinary dentistry. Vet Clin North Am Small Anim Pract 32:791-837, 2002, with permission.)

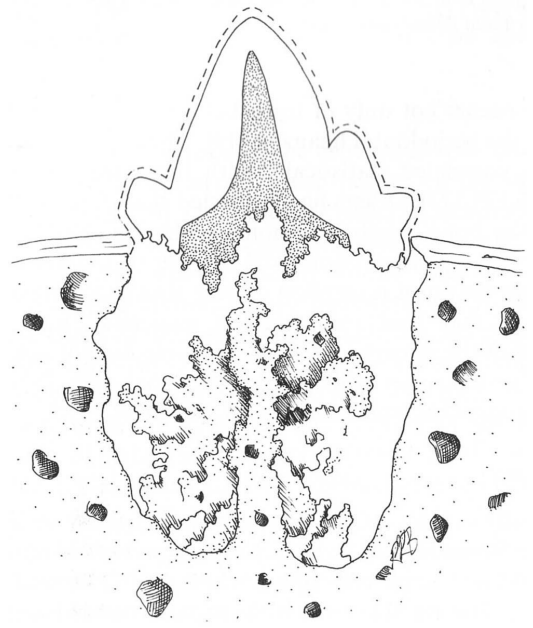

Figure 9-14. Stage 5b feline odontoclastic resorptive lesion with extensive root replacement resorption and a nearly intact crown. (Illustration by Rebecca Rae Bradford. From Reiter AM, Mendoza K: Feline odontoclastic resorptive lesions. An unsolved enigma in veterinary dentistry. Vet Clin North Am Small Anim Pract 32:791-837, 2002, with permission.)

and E do not involve the endodontic system; however, types B, D, and F do expose pulp tissue.[93]

HISTOPATHOLOGY

The first pathology reports on feline resorptive lesions appeared in the 1920s.[14,15] In the mid 1950s, they were reported as carious lesions.[2-4] In the 1970s, two histopathological studies described tooth resorption, and it became obvious that resorptive lesions were not caries.[5,21,94]

Resorptive Phase

Feline resorptive lesions start on root surfaces, which face the periodontal ligament and progress from root cementum into crown dentin. The enamel becomes undermined as the lesions progress. The enamel then is resorbed or loses contact with the underlying dentin and breaks off. The edges of the defects are lined with odontoclasts surrounded by infiltrating macrophages, white blood cells, and fibroblasts. Rounded cells also are present, likely resting osteoblast-type cells adjacent to odontoclasts. Odontoclasts resorb dentin and cementum and create resorption lacunae and canals in hard dental tissues. Resorption of alveolar bone also occurs when the periodontal ligaments are damaged.[38,39]

Reparative Phase

Reparative and resorptive phases occur simultaneously. During reparative processes, cementoblast-type or osteoblast-type cells produce a hard tissue, which resembles osteoid, bone, cementum, bone-cementum, and osteodentin to replace the damaged dentin. Odontoclasts prefer to attach to intact dentin and not the newly formed reparative tissue. Odontoclasts may prefer the more mineralized intact dentin.

Pulp Response

In advanced resorptive lesions, the pulp is not involved until late in the process. Once the predentin is involved, odontoblasts degenerate and pulpitis becomes gradually progressive. Reparative dentin (tertiary dentin) may be produced by the odontoblasts. Younger animals tend to have more reparative dentin. Reparative dentin was never found in Stage 1 lesions, but 69 per cent of stage 2 lesions and 31 per cent of stage 3 lesions showed evidence of reparative dentin.[19,69]

DIAGNOSIS

Clinical Signs

Cats with FORLs can present with anorexia, dysphagia, halitosis, ptyalism, dehydration, lethargy, discomfort, and weight loss. Most affected cats do not show distinct clinical signs. Sneezing, excessive tongue motions, and head shaking also have been observed. Spontaneous repetitive motions of the jaw may be seen during grooming or eating and drinking. Oral pain may appear as dropping food, refusal of hard food, running from food, hissing when eating, and possibly aggression. Pain is associated with dentin exposure. The lesions may be asymptomatic when the resorption process is taking place below the gingival attachment without affecting the pulp. Clinical signs may occur when pulpitis develops or when the lesion emerges at the gingival margin.

Oral Examination

FORLs often are covered with calculus or plaque, hyperplastic gingiva, or granulation tissue. The lesions are found most often at the gingival margin near the cementoenamel junction, in the furcation area of multirooted teeth (Figures 9-15 through 9-17).

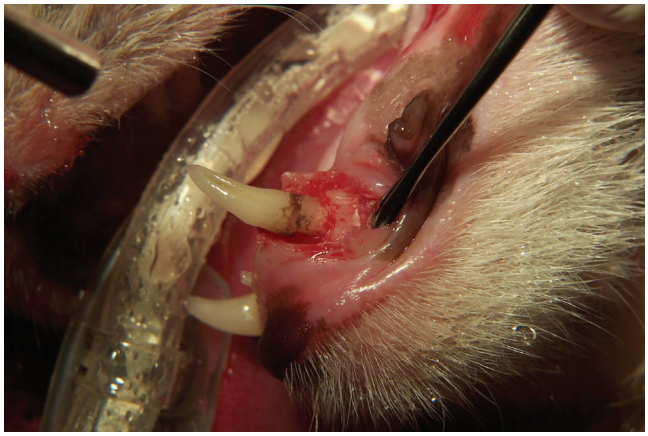

Figure 9-15. Root surface resorption on the left mandibular canine tooth (304).

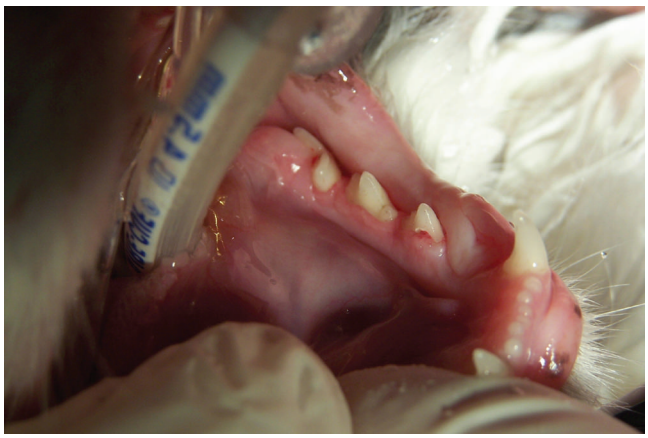

Figure 9-16. Resorptive lesion at the lingual furcation of the left mandibular third premolar (tooth 307).

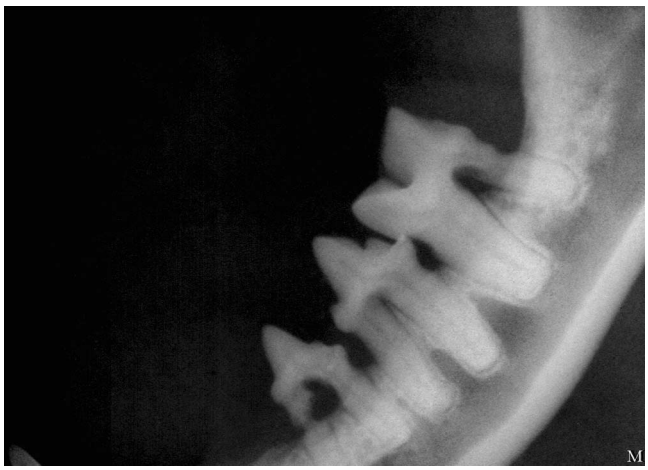

Figure 9-17. Radiograph of the left mandibular third premolar (tooth 307) in Figure 9-16.

In the advanced stages of disease, the lesions penetrate the pulp, leading to pain and fracture of the crown with loss of the crown. Osteoblastic activity can cause thickening of the alveolar wall, and root exposure results from "supereruption." Root exposure may contribute to the development of FORLs, and gingival

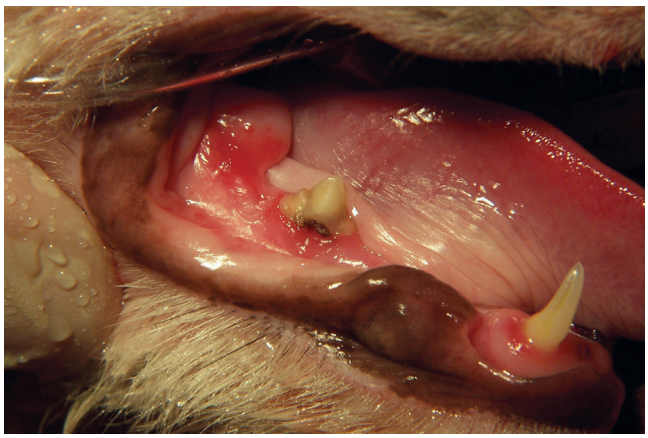

Figure 9-18. Resorptive lesion at the buccal furcation of the right mandibular fourth premolar (tooth 408). Note missing crowns of the third premolar (tooth 407) and molar (tooth 409).

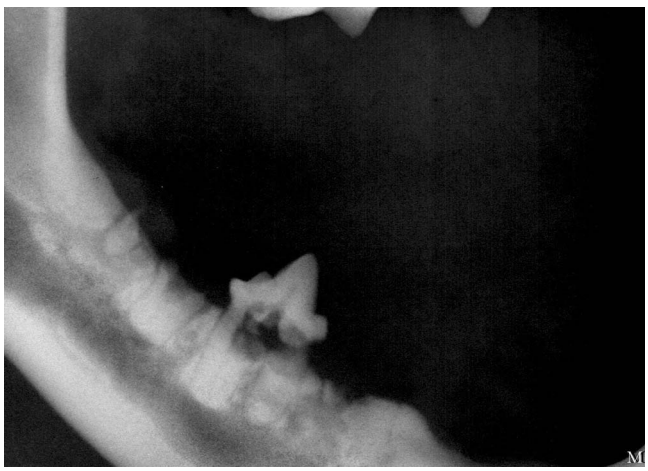

Figure 9-19. Radiograph of the right mandibular fourth premolar (tooth 408) in Figure 9-18. Note the retained roots of the third premolar and molar.

recession around the canine teeth may result from odontoclastic root resorption.

Radiographic Findings

Intraoral dental radiographs provide information about the structure of the tooth and the extent of FORLs.[10,95-97] Visual clinical examination and correct radiographic interpretation, correlated with the patient's history and appropriate laboratory values, are necessary to achieve excellence in patient diagnosis and treatment. FORLs can appear as subtle changes in the tooth structure at the furcations or cementoenamel junction. Some roots may appear as ghosts or tooth structure fused to bone. Alveolar bone may appear densely sclerotic or irregular (Figures 9-18 to 9-25).

In evaluation of periodontal disease, the main objective is to evaluate bone loss around one or more roots and furcation involvement. Vertical bone loss exists when the level of bone adjacent to the root is more apical than the interdental bone level. Horizontal bone loss exists when the level of bone is at a consistent level around the involved teeth. Furcation involvement in multirooted teeth is graded. Grade I indicates no

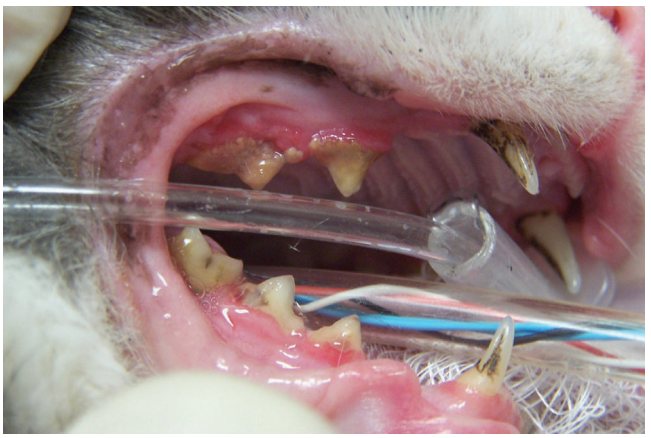

Figure 9-20. Dental calculus covering resorptive lesions in the right maxillary fourth premolar (tooth 108).

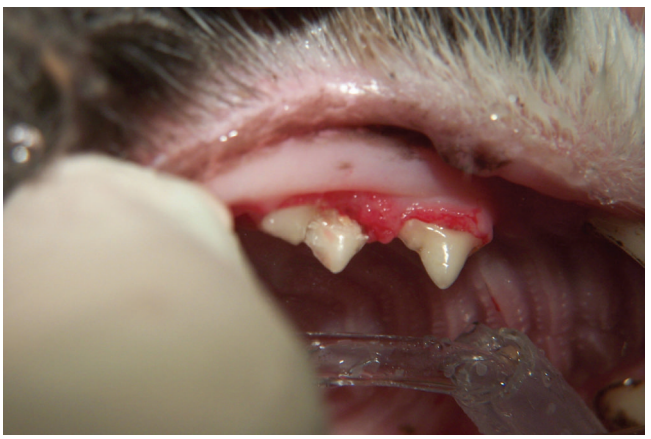

Figure 9-21. Resorptive lesions (in Figure 9-20) in the right maxillary fourth premolar (tooth 108) become apparent after ultrasonic scaling.

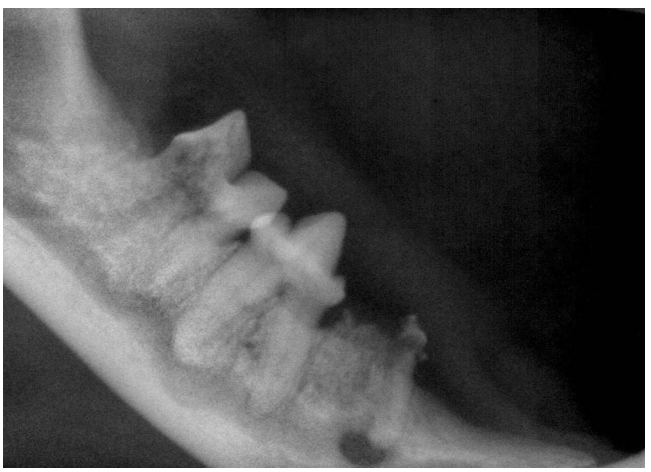

Figure 9-22. Radiograph of resorptive lesions in the right mandibular third premolar (tooth 407) and molar (tooth 409) of the cat in Figure 9-1.

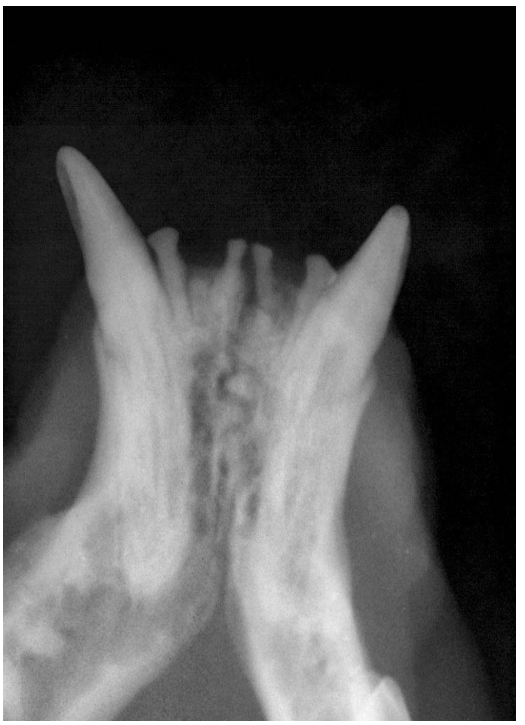

Figure 9-23. Radiograph of the mandibular canine teeth with root replacement resorption.

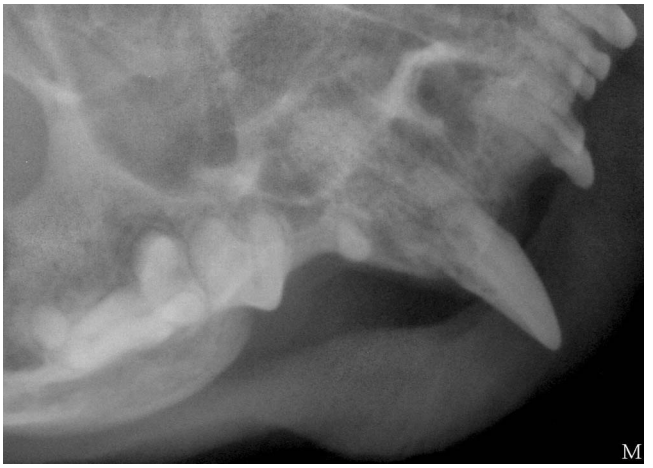

Figure 9-24. Radiograph of the right maxillary canine tooth with root replacement resorption.

radiographic changes. Grade II is associated with thinning of bone at the furcation on one side but with no connection to the opposite side. Grade III shows complete loss of bone at the furcation between both sides of the tooth. An apical lucent area at one or more tooth roots can be seen with either endodontic or periodontic involvement of the tooth, or with combinations called endo-perio or perio-endo lesions.[98-103]

When a resorptive lesion is seen clinically, a dental radiograph can reveal whether the lesion involves the pulp tissue, if periapical changes exist, and if the resorptive defect is diffuse. Root remnants can be visualized, and evidence of root ankylosis can be appreciated with proper dental radiographs. Fusion of the root cementum surface and the alveolar bone is termed dentoalveolar ankylosis—a form of replacement resorption in which the cementum slows the replacement of dentin with bone. The root structure becomes irregular or disappears. In root replacement resorption, the root dentin is replaced by bone. As resorption progresses into a tooth, a mottled or

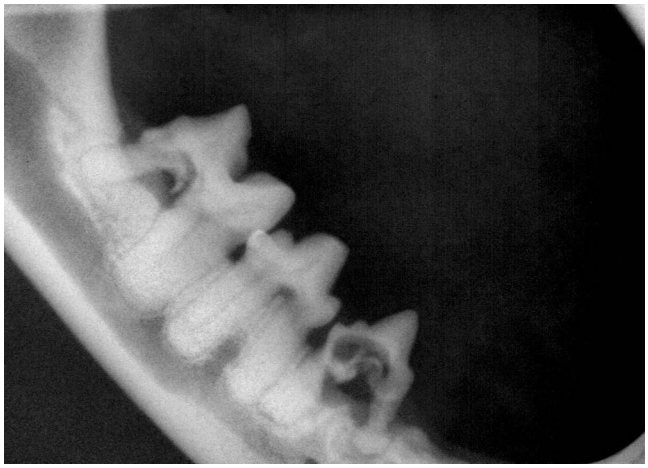

Figure 9-25. Radiograph of the right mandibular third premolar (tooth 407) and molar (tooth 409) with a resorptive lesion at the furcation.

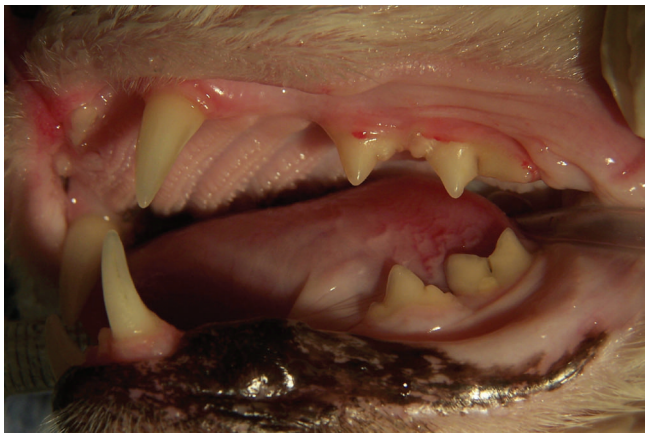

Figure 9-26. A glass ionomer filling placed at the left mandibular molar (tooth 309) near the buccal furcation area.

striated appearance is visible. Fragments of tooth structure may be seen with radiographs and must be removed to prevent osteomyelitis. Clinically small resorptive lesions may involve the entire tooth diffusely, and dental radiographs are the only technique that allows visualization of the extent of resorption.

TREATMENT

Restoration

Because of poor long-term success in treating resorptive lesions with restorations, this treatment is now chosen rarely for teeth with resorptive lesions. Stage 1 lesions often are too small to restore, and Stage 2 and 3 lesions often have restoration failure because the resorptive process continues under the restoration within the tooth structure (Figure 9-26). Restoration cannot be considered in Stage 4 and 5 lesions because of extensive tooth structure loss. Restoration cannot be recommended based on results of long-term studies, which show evidence of further progression of resorption.[7,9,12,104-108]

Fluoride Treatment

Fluoride has anticariogenic properties: inhibiting plaque formation, increasing the microhardness of enamel and dentin, and desensitizing the teeth. Fluoride inhibited osteoclasts in vitro and suppressed root resorption in rats, but it has never been shown to prevent or slow resorption in affected cats. If it is applied, a fluoride varnish, sealant, or bonding agent is recommended and should be placed after the teeth are cleaned and polished. Fluoride treatment remains controversial because the underlying etiology of resorptive lesions has not been determined.[109,110]

Superficial resorption that involves only dentin and the overlying adjacent enamel of the crown without pulp tissue exposure may be smoothed with a fine white stone or diamond bur. A fluoride-releasing sealant then is applied and possibly in combination with a weekly application of fluoride homecare gel. Fluoride has been used for its desensitization and antiplaque properties, and because it makes the mineral component of the tooth surface more resistant to dissolution. Fluoride treatment has not been shown to be effective in the treatment of resorptive lesions, and concerns exist about fluoride toxicity in cats. Once the resorptive process extends deeper into the dentin and pulp, extraction is the best option to relieve the patient's pain.

Alendronate

Based partially on the information about vitamin D activity and the development of resorption lesions, a study by Harvey was completed to evaluate the use of alendronate (Fosamax–Merck, Whitehouse Station NJ), which binds to periodontal bone and tooth root surfaces in cats, to treat and prevent resorption.[111-113] The preliminary findings of this research suggested that alendronate decreased the progression of FORLs and prevented additional formation of resorptive lesions. The assertion that alendronate slows or arrests progression of resorptive lesions is premature and is not justified by the data presented thus far.

The Harvey study actually included three studies.[113] In the first study, the tissue distribution of alendronate was evaluated over a period of 24 hours after a single intravenous bolus injection in three cats. In a second study, the oral bioavailability was studied indirectly 24 hours after oral administration in 12 cats; three different drug formulations were used at weekly intervals. These first two studies (tissue distribution and bioavailability) provided valuable information. In the third study, nine cats with FORLs were treated with either alendronate or a placebo and were evaluated radiographically. The combination of the first two studies failed to determine the optimal dosage, recommended treatment interval, and most suitable formulation of the drug. Also a limited number of subjects were used in each study, and gender limitation was present. Only female cats, most of which were spayed, were used in the three studies. Another major concern is the fact that the number of cases used in this study was small (four controls, five treated; 14 teeth in total). A more definitive study should involve a large number of patients over a period of years.

The third part of the Harvey study about progression of FORLs is difficult to follow.[113] The authors point out correctly that further work is needed, but they do not discuss what is really learned from the projects they report. For example, it has been observed clinically that the progression of resorptive lesions is sporadic, with significant interpatient and intrapatient variability.

Long-term treatment with alendronate requires a palatable preparation. The assigned treatment should be stable

throughout the course of study, and animals that deviate substantially from the assigned regimen should be withdrawn. The oral dosage used in the Harvey study was 9 mg/kg PO twice weekly in a 5:1 tuna:alendronate mix.[113]

The Harvey studies must be considered as pilot projects. The objective of a pilot study is to refine technique and experimental design and to revisit initial ideas about how to analyze the data. Hopefully alendronate will prove to be a useful treatment, but that conclusion cannot be drawn from the currently available data.

Laser Therapy

Resorptive lesions have been treated with neodymium:YAG laser, including enameloplasty and gingivoplasty, with the thought that laser energy may evaporate the surface odontoclasts and modify the tooth surface structure to prevent reattachment of odontoclasts and progression of the resorptive process. Some of these treated teeth developed resorption around the previously laser-treated areas or developed resorptive lesions on other areas of the tooth. Irreversible pulp and nerve damage can occur because these teeth are exposed to excessive heat. Further studies with radiographs and histopathology are needed to substantiate absence of progression of resorption in laser-treated teeth. Because concerns exist about damage to associated tissues, laser therapy cannot be recommended as a mainstream treatment for affected cats.[114-116]

Electrocautery cannot be recommended as a treatment of FORLs because of the same effects of collateral heat damage seen during laser application.

Extraction

Conventional nonsurgical extractions are difficult or impossible in teeth affected by resorption unless concurrent advanced periodontal disease is present. The resorbing root structure is brittle, and the bony ankylosis that replaces the periodontal ligament no longer allows mobilization of the tooth. Attempts to mobilize and elevate the tooth often result in fragmentation and incomplete removal of the roots.

Surgical extraction techniques allow the complete removal of the tooth structure. A full-thickness mucogingival flap is elevated and reflected on the buccal/labial side of the tooth to expose the bone. The buccal plate of alveolar bone overlying each root is removed carefully using a bur in a high-speed, water-cooled dental handpiece until at least half of the root is visualized. Multirooted teeth are sectioned with the bur, and the individual root segments then are elevated carefully. The alveolar ridges are smoothed with the bur and the gingiva is closed with fine, absorbable sutures.

Extraction of teeth with advanced FORLs is the best choice of therapy. The cause of resorptive lesions is unknown, and these lesions are progressive and painful. The goal of treatment is to create a healthy, pain-free mouth, and the persistent inflammatory processes associated with resorptive lesions must be removed. Retained damaged tooth structures lead to chronic oral inflammation, bone sequestrum, alveolar osteitis, and osteomyelitis.

Teeth with resorptive lesions often are brittle and break easily, which makes extraction difficult. When the crown is not present, the root remnants often are ankylosed, which makes differentiation between root structure and alveolar bone difficult. A mucoperiosteal flap is recommended to allow visualization of the root remnants. Once the roots are removed, the alveolar ridge is smoothed and the extraction site is sutured with absorbable suture material.

A high-speed, water-cooled dental handpiece with a small, round bur can be used to remove root remnants by drilling away the tooth structure or "atomization" of these roots. Many veterinarians have learned this technique of "burring out the roots." Incomplete removal of tooth structure by this method is common, and radiographs must be taken to confirm the complete removal of root structures. This procedure often fails to remove all of the root structure and carries with it the risk of complications from misdirection of the bur, transport of root remnants into the nasal cavity or mandibular canal, or damage to neurovascular structures and alveolar bone. Other complications include the introduction of contaminated oral fluids into the alveolar bone, mandibular canal, nasal sinus, or suborbital space and creation of subcutaneous or sublingual emphysema and air emboli from the pressurized air used with drilling.

Some dental specialists believe that root remnants without periapical pathology may be left in place, although others recommend removal because these remnants may lead to persistent inflammation.[1,9,62,117] These remnants become incorporated into the normal remodeling process and eventually the tooth structure is replaced by bone. Intentional root retention after crown amputation has been advocated for teeth undergoing resorption. This alternative should be considered only for patients in which no evidence exists of discomfort, gingival inflammation, or fistula formation. Crown amputation with intentional root retention as an alternative to extraction of the entire tooth structure may be recommended in select cases in which no evidence exists of periapical pathology on dental radiographs or clinical gingivostomatitis.[117] If cats are infected with FeLV or FIV, extraction of the entire tooth is recommended. Follow-up with dental radiographs is recommended to monitor the continued tooth resorption.

SUMMARY

The most common disease of the domestic cat is a resorptive lesion of the teeth. The preferred term, which reflects the process of tooth destruction, is feline odontoclastic resorptive lesions (FORLs). The etiology of FORLs is still under investigation, and recent studies indicate a dietary influence associated with calciotropic hormones.[1,32-34] However, the exact causative factors leading to the development of resorptive lesions are still not known. One third of cats may develop FORLs during their life and risk increases as cats age. Extraction of teeth with advanced resorptive lesions is the treatment of choice.

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Chapter 10

Esophagitis and Esophageal Strictures

Michael D. Willard

Esophagitis and benign esophageal strictures often are missed in cats because awareness of the problem is low, the clinical signs are not unique, and the diagnosis typically requires more than plain radiographs and routine clinical pathology testing. The true incidences of esophagitis and benign strictures are unknown, but a busy practice should expect to see a few cases each year. Because esophagitis often is not suspected and consequently is not treated in a timely fashion, strictures can occur and make management more expensive and complicated.

ESOPHAGITIS

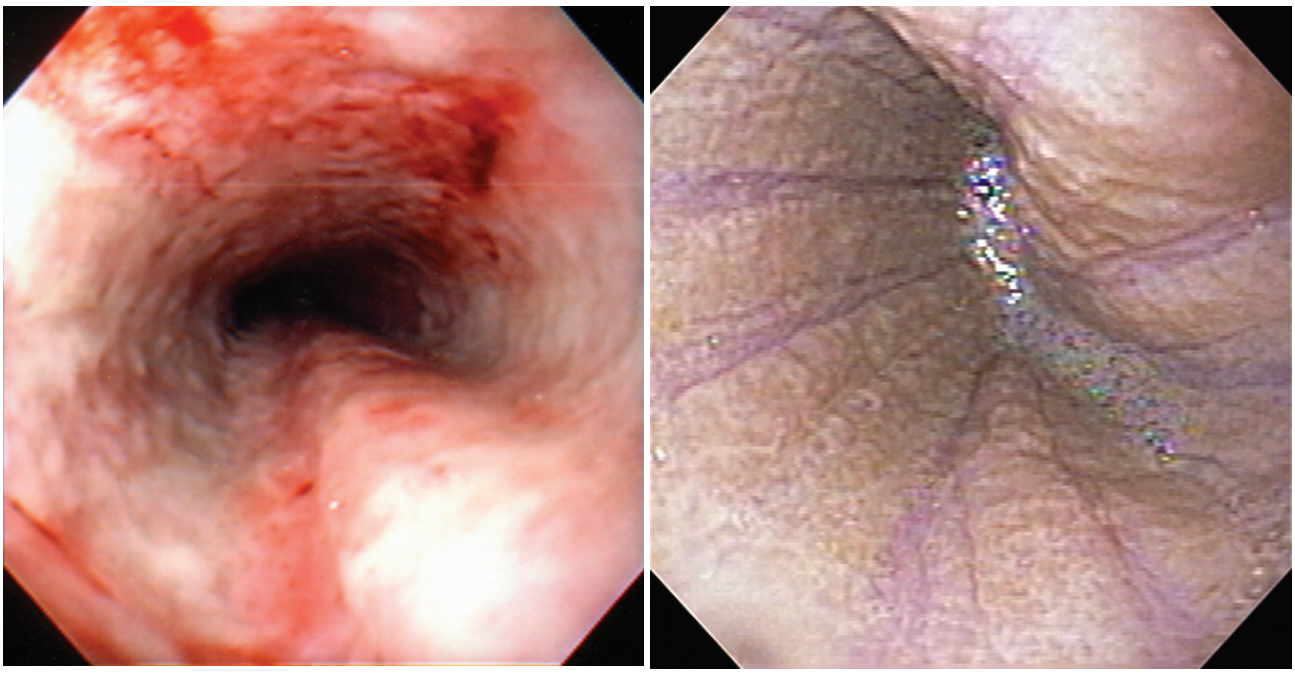
Esophagitis can cause a wide spectrum of clinical signs.[1] Cats with mild esophageal inflammation may simply spit up food and/or phlegm from time to time. Usually the expelled material contains no hint of blood. More severely affected cats may regurgitate everything they eat and can experience so much esophageal pain that they are reluctant to eat. Sometimes esophagitis can be so excruciatingly painful that patients do not even swallow saliva. In the latter cases, spontaneous gulping movements may provide an important clue about the possible presence of esophagitis. The clinician typically does not expect to see fever or a high peripheral white blood cell count, but such changes could occur. Although aspiration pneumonia is a possible complication of any esophageal disease, it apparently is not as common in cats with esophagitis compared with those with megaesophagus. Megaesophagus typically is not expected in dogs with esophagitis but can be seen in some cats with this disease.

Esophagitis usually is caused by foreign objects that have lodged in the esophagus (e.g., hairballs), improper administration of caustic medications (e.g., tetracycline), gastroesophageal reflux, and excessive vomiting from any cause (especially gastric outflow obstruction).[1,2] Although cats have more discriminating eating habits and do not suffer from esophageal foreign objects as frequently as dogs, hairballs expelled from the stomach and lodged in the esophagus are a potential problem. Hairballs can be abrasive to the esophageal mucosa and cause significant trauma. The hairball can remain in the esophagus, eventually be regurgitated, or migrate back down to the stomach. The history can be misleading without careful determination of whether the cat is vomiting or regurgitating. Unfortunately, some feline vomiting caused by gastric or intestinal disease looks exactly like textbook regurgitation. However, if the act sounds like it changed from periodic vomiting to more constant regurgitation, the clinician should be suspicious of esophagitis.

Pills and capsules can lodge in the esophagus for minutes or more than an hour if they are not followed by water or food.[3] These pills can lodge anywhere, but the cervical esophagus appears to be the most common site. Administration of caustic medications, tetracyclines in particular, seems to be a significant cause of esophagitis in cats.[4] Tetracyclines, including doxycycline, are used commonly in cats in many parts of the United States as a result of our expanding knowledge of infectious diseases responsive to these medicines. Indeed, the axiom that "no pet should die without the benefit of steroids" has been replaced (in some places, at least) with "no pet should die without the benefit of doxycycline." The validity of this statement notwithstanding, it is a testament to the frequency with which these drugs are used. However, tetracyclines are not the only drugs with the potential to cause problems. Nonsteroidal antiinflammatory drugs (NSAIDs) can do likewise,[5] and many others probably could be responsible (especially capsules and noncoated tablets). Finally, caustic substances licked off of their fur (e.g., benzalkonium chloride[6]) also can be responsible.

Repeated or prolonged exposure of the esophageal mucosa to gastric acid can cause esophagitis. Anecdotally, the feline esophagus seems more sensitive to the adverse effects of gastric acid than the canine esophagus. Gastric-outflow obstruction can cause repeated vomiting of large amounts of gastric acid, which ultimately produces megaesophagus, ostensibly resulting from esophagitis caused by repeatedly "bathing" the esophagus with the large volumes of gastric acid.[7] Resolution of the gastric outflow obstruction in affected cats may be associated with disappearance of the megaesophagus.

Spontaneous gastroesophageal reflux is documented poorly in cats, although hiatal hernias seem a likely potential cause. Although many hiatal hernias are asymptomatic, some are associated with substantial gastroesophageal reflux.[8] In distinction, intraoperative gastroesophageal reflux is known to happen. It is a rare albeit important cause of esophagitis.[9,10] Uncommon,



A B

Figure 10-1. A, An endoscopic view of the esophagus of a cat with obvious esophagitis. Note the obvious hemorrhage. **B,** An endoscopic view of the esophagus of a cat with severe esophagitis. This esophagus is covered with a pseudomembrane that, when scraped off, revealed a hyperemic, hemorrhage mucosa.

unpredictable, and not immediately obvious, its significance to the clinician centers on the fact that it is iatrogenic, brought on by anesthesia for surgery. Therefore it often is considered the veterinarian's fault. If a patient has a poor appetite within 1 to 2 days of any anesthetic procedure, and especially if the patient starts to regurgitate/vomit during that time, iatrogenic esophagitis could be the cause. If esophagitis has occurred during anesthesia, early detection and treatment are paramount to make a favorable outcome more likely and easier to obtain.

Diagnosis

A complete blood count and serum biochemistry profile typically show nothing of significance unless it is from the primary cause of the vomiting. Plain thoracic radiographs usually are normal, although megaesophagus may be seen in some cats. Contrast radiographs may reveal very subtle changes (e.g., excessive barium retained on the esophageal mucosa) or obvious esophageal weakness. Fluoroscopy sometimes reveals decreased esophageal function, but it can be subtle in some affected cats.

In most cases, diagnosis is based upon the endoscopic appearance of the esophageal mucosa,[1,2] which usually is red, friable, and roughened (Figure 10-1). In many affected cats, spontaneous bleeding or hemorrhage is seen after routine contact between the surface of the endoscope and the esophageal mucosa, something that is absolutely not expected in an otherwise normal feline esophagus. Hiatal hernias can be subtle, and the clinician should examine the lower esophageal sphincter carefully from the orad and aborad sides. This involves retroflexing the tip of the scope in the stomach to examine the fundus and cardia in detail.[2]

In some cases, esophageal mucosal biopsy may aid in diagnosis.[11,12] How frequently biopsy is required for diagnosis of feline esophagitis is unknown. Biopsy of the esophageal mucosa with a flexible endoscope is more difficult than biopsy of gastric or intestinal mucosa. The smooth-muscle portion of the esophagus usually can be biopsied with flexible endoscopes (assuming a forceful grasp of the mucosa). However, normal feline cervical esophagus can be impossible to biopsy with a flexible endoscope. The stratified epithelial mucosa of the cervical esophagus and the difficulty in grasping a fold of mucosa in this region make it difficult to obtain a diagnostic piece of tissue, unless substantial disease is present. Older biopsy devices (e.g., Rubin tube) obtain esophageal mucosa reliably, but they are seldom used.

Treatment

When esophagitis is found, the clinician first should determine the reason for its presence instead of its method of treatment. If an untreated, underlying cause exists, all the medications administered are likely to be wasted. A complete upper gastroduodenoscopy with multiple gastric and duodenal biopsies is mandatory unless a cause is obvious (e.g., mass at pylorus). Even if a foreign body is found, it is still wise to biopsy the stomach and duodenum. Although almost all gastric foreign bodies in vomiting cats are the cause of the vomiting, we occasionally see foreign bodies present that are not causing any problems. In case of any doubt, biopsies obtained from a patient can be stored until it becomes obvious whether the vomiting will stop after removal of the foreign body.

Treatment consists of removal or treatment of the cause, if known, and then protection of the denuded esophagus from any further exposure to gastric acid.[13] Once esophagitis is present, normal esophageal function likely can be sufficiently disrupted so that the lower esophageal sphincter tone is lessened,[14] which predisposes to gastroesophageal reflux. This decrease in lower

esophageal tone apparently can then initiate a positive feedback cycle in which inflammation leads to disrupted motility, which allows reflux of acid into the esophagus, which makes the inflammation worse, which makes the motility worse, and so on. Although gastric mucosa is somewhat resistant to the effects of gastric acid, denuded esophageal mucosa is exquisitely sensitive to even minute amounts of acid. Decreasing production of gastric acid aggressively in patients with esophagitis is more important than in those cats with gastric erosions or ulcers.[15]

Use of antacid drugs to minimize gastric acid production is referred to as chemical clearance. Histamine-2 receptor antagonists (H-2 RAs) such as cimetidine, ranitidine, and famotidine are used commonly for this purpose. They are helpful drugs; however, they are competitive inhibitors of gastric acid secretion. The fact that they are competitive as opposed to noncompetitive means that although they lower gastric acid secretion, they are minimally effective at abolishing it. Many cats can be treated successfully with H-2 RAs. The H-2 RAs are relatively inexpensive and can be administered parenterally, a distinct advantage in treatment of a vomiting/regurgitating cat. However, some cats require greater gastric acid suppression than is possible with H-2 RAs.

Because proton-pump inhibitors (PPI) are noncompetitive gastric acid suppressants,[15,16] they usually are more effective than H-2 RAs at healing esophagitis. The PPIs generally must be administered orally, which can be a disadvantage. Therefore PPIs generally are reserved for the more severely affected patients or those that have resisted the effects of H-2 RAs. These patients often have gastrostomy tubes inserted, which eliminate problems associated with administration of oral medications to regurgitating patients. Omeprazole is not approved for use in cats, but it has been used for this purpose. Since omeprazole has become an over-the-counter drug, its cost has decreased. A typical dose is 0.7 mg/kg PO q24h, but I have used doses as high as 2 mg/kg q24h for more than a year without complications. The safety of this dose has not been established. Anecdotal reports exist of using lansoprazole, but no dose has been established.

Volume clearance means keeping the stomach empty of all secretions. Gastric fluid contains digestive enzymes that could potentially delay healing of denuded esophageal mucosa. Volume clearance is best accomplished by stimulating normal gastric outflow via the pylorus[13] with prokinetic drugs. Formal studies of the efficacy of prokinetics in cats with esophagitis are lacking, but such drugs are beneficial in affected human beings. Metoclopramide is the most commonly used prokinetic drug in cats and has a long track record of safety. Cisapride is considered a more effective gastric prokinetic than metoclopramide,[17] and it tightens the lower esophageal sphincter, an action that helps prevent gastroesophageal reflux. No longer marketed for human medicine, many veterinary pharmacies that compound drugs can provide it if given a prescription. Although cisapride is a more effective gastric prokinetic than metoclopramide, it must be given orally. Ranitidine has some prokinetic effects, but how they compare to metoclopramide and cisapride in cats is unclear.

In severely affected patients, especially those that continue to regurgitate or those that refuse to eat, endoscopic placement of a gastrostomy feeding tube often is helpful. Such a tube allows adequate nutritional support in addition to a means of medication administration (e.g., omeprazole, cisapride, H-2 RAs, and metoclopramide) when the patient goes home and is treated by the client. If such a tube is placed, the clinician should seek to minimize further trauma to the esophagus during the placement procedure. Esophagostomy and pharyngostomy tubes should not be used in these circumstances, because having the feeding tube in contact with the eroded esophageal mucosa probably impedes healing (see Chapter 16).[18]

The use of corticosteroids in these patients is controversial. Although it makes intuitive sense that administration of corticosteroids decreases inflammation and thereby lessens the risk of subsequent stricture formation, no positive proof exists that this occurs in human patients with severe esophagitis from corrosive injury.[19] Empirical use of corticosteroids typically is reserved for cats with especially severe esophagitis, in which the risk of stricture is deemed great enough to take whatever steps might prove to be helpful. Typically, we have used anti-inflammatory doses of dexamethasone (0.11 mg/kg) given parenterally every 2 to 3 days.

Sucralfate slurries or suspensions have been used in these affected cats in the hope that they would be as helpful for esophageal erosions as they are for gastric erosions. The efficacy of carafate for esophagitis is unknown, but no benefit has been seen in human patients with severe esophagitis.[20] Using carafate makes intuitive sense. Seemingly carafate should be helpful in cases of gastroesophageal reflux, because reflux results in gastric acid present in the esophageal lumen, a prerequisite for carafate attaching to eroded mucosa. Antibiotics also have been used in these patients, but their efficacy is unproven.

BENIGN STRICTURES RESULTING FROM CICATRIX

A benign stricture resulting from fibrous connective tissue may be the consequence if esophagitis is severe, especially if the submucosa is damaged. The location of a stricture seems somewhat dependent upon the cause. Gastroesophageal reflux primarily causes strictures from near the heart base to the lower esophageal sphincter, whereas caustic pills lodge commonly in the cervical esophagus, and foreign bodies often lodge at the thoracic inlet, base of the heart, or near the lower esophageal sphincter. Very rarely, a stricture may occur at the site of an esophagostomy tube after removal of the tube. This complication happens seldom enough that the clinician should not hesitate to use esophagostomy tubes but also should not be complacent if the patient begins to regurgitate after removal of the tube. Strictures typically result in regurgitation of solid food but may or may not cause regurgitation of liquids, depending upon how large of an opening is present in the stricture. A stricture may develop and cause regurgitation within days of the initiation of esophagitis, or it may not be evident for a week or more. Regurgitation beginning a few days or a week or more after an anesthetic procedure or treatment with tetracycline is suggestive of a stricture.

Diagnosis

Although contrast radiographs can be diagnostic (Figure 10-2), they also may miss partial obstructions if the opening in the stricture is large enough to allow liquid barium to pass through before the radiograph is exposed. Administration of barium (especially when mixed with food) in association with

fluoroscopy should allow the clinician to find any esophageal stricture, but few clinicians have access to fluoroscopy.

Endoscopy (Figure 10-3) is the preferred way to diagnose strictures[1,2]; generally, it is more sensitive at finding strictures than radiographs are (assuming the endoscopist is experienced) and also allows correction of the stricture at the same time. However, it is possible to pass a very small–diameter endoscope through a stricture without realizing that a narrowing existed (although this usually is more of a problem in dogs than cats because of the size of the patients). A possible complication associated with endoscopy includes inadvertent insufflation of too much air into the esophagus, which then passes into the stomach and causes bloat. If the cat will not eructate and the endoscope cannot be passed into the stomach (which is typical in these cases), then the clinician may have to trocharize the stomach to relieve the pressure. The clinician also must be careful during endoscopy not to push the tip of the scope into the stricture with too much force and rupture the esophagus (Figure 10-4). One of the basic tenets of endoscopy is to always "look where you are going and not advance the tip of the endoscope blindly"; obeying this principle will prevent such complications. Many strictures are found within centimeters of the cricopharyngeus; therefore the clinician cannot pass the endoscope blindly a few inches into the esophagus and then start to observe.

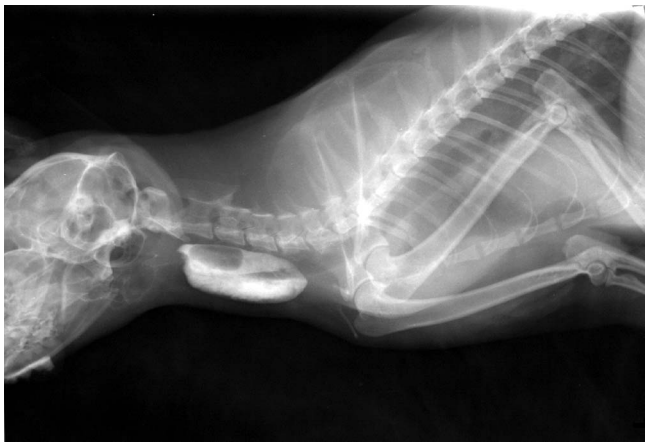
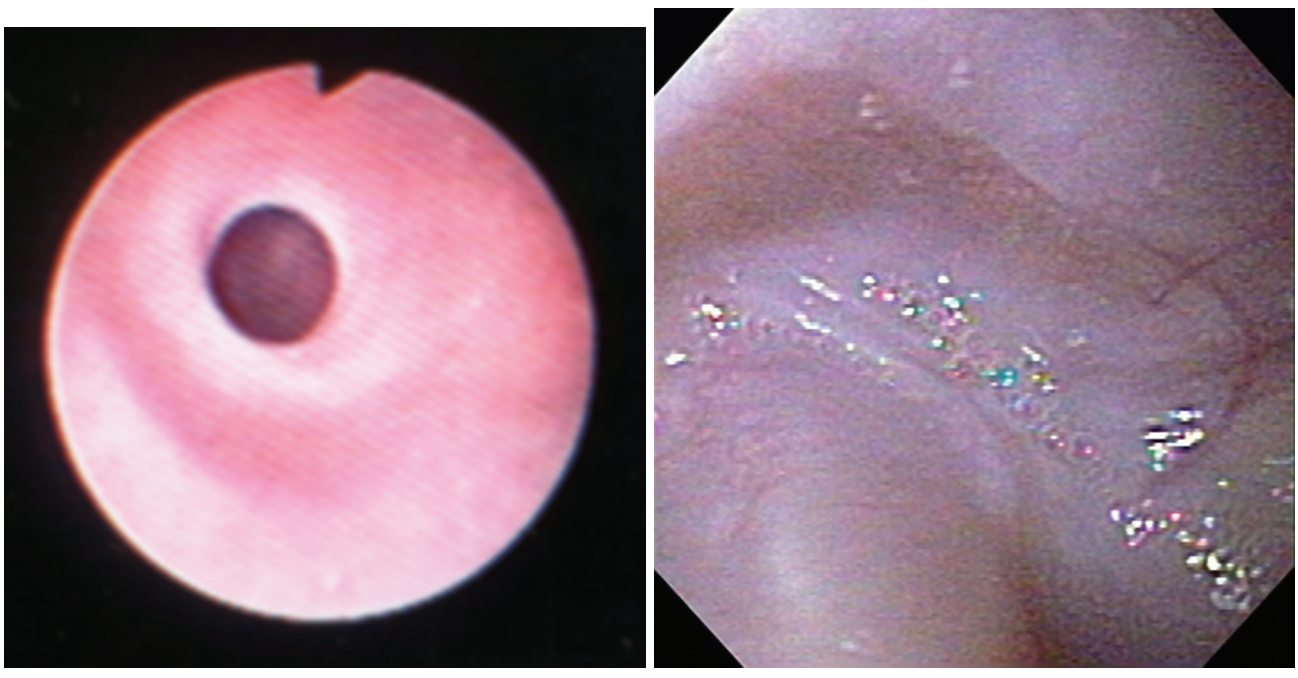


Figure 10-2. A radiograph of a cat after administration of barium. A complete stricture is present in the esophagus (see Figure 10-3, *B*).

Treatment

Once a stricture is found, dilation with either a bougie or a balloon catheter typically is the next step.[1,2] Strictures can be resected surgically, but the likelihood of stricture reformation and the desire to avoid a thoracotomy make dilatation the preferred approach. Although the goal of esophageal dilatation is to return the esophagus to normal, making the esophagus functional when eating either regular food (most desirable) or softened (not gruel) canned food typically is adequate. The clinician must seek to cause the least amount of trauma possible while tearing open the stricture. The esophagus heals rapidly, and the stricture easily can reform within days. Indeed, if one causes excessive trauma (e.g., causing a very deep break extending well into the submucosa, stripping off excessive mucosa during aspiration, moving the endoscope or balloon over the site repeatedly), then the likelihood of stricture reformation is that much greater. The less trauma caused by the dilatation, the less likely the stricture will reform. Also, the less severe the stricture is to begin with, the less likely that excessive trauma will occur during the dilatation. Therefore early diagnosis of strictures probably is advantageous.

Although balloon catheters have been promoted as superior to mechanical bougies because they do not cause the shear



A **B**

Figure 10-3. A, An endoscopic view of a benign partial stricture caused by prior esophagitis. **B,** An endoscopic view of a benign complete stricture caused by prior esophagitis.

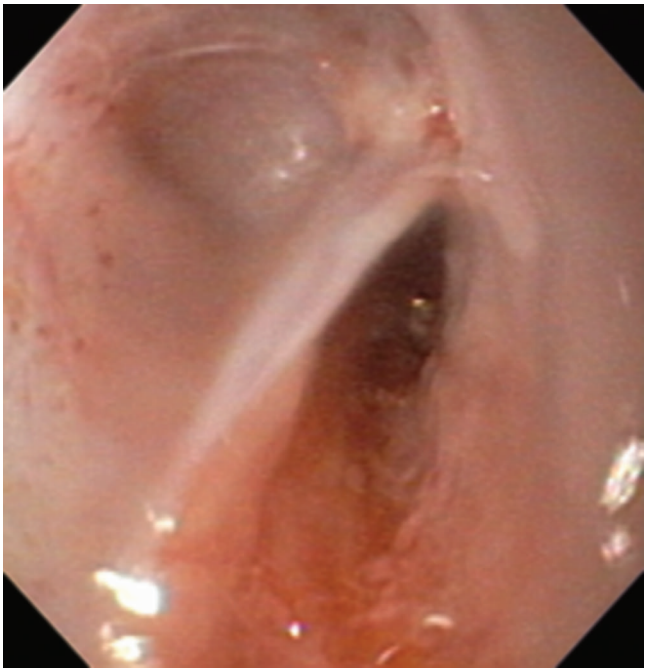


Figure 10-4. An endoscopic view of the esophagus of a cat with a benign stricture. The endoscope was pushed into the stricture too hard, and a diverticulum is obvious. If more pressure had been applied when advancing the scope, perforation likely would have resulted. (Used with permission. Vet Clin North Am Small Anim Pract 33:945-967, 2003.)

forces associated with bougienage, no good evidence exists that one technique is superior in human patients with such strictures, assuming that the operator is trained in their use.[21] Esophageal dilation catheters typically have a balloon that is 12 to 22 mm long. Having such a long balloon is advantageous, and other devices with round balloons (e.g., endotracheal tubes) often are poor substitutes. If a round balloon is used to try to rupture a relatively tough stricture, the balloon often migrates in or out of the stricture while being filled with air or water, with the result that the esophageal stricture is not ruptured. The longer balloon is much more likely to stay in the stricture as it is being filled with air or water, which forces the stricture to rupture.

Balloon catheters can be placed through the endoscopic biopsy channel (usually requires a 2.8-mm biopsy channel), down a preplaced guidewire, or along side of the endoscope.[1] The balloon should be placed so that the stricture is at the middle of the balloon. Then the balloon is distended with either air or water. Caution is necessary not to exceed the stated maximum pressure of the balloon. Dilating the stricture typically is painful, and the clinician usually sees an increased respiratory rate when the stricture is being torn. Some bleeding usually occurs, but it is expected to be minor. The clinician typically starts by using a 10- or 15-mm balloon, depending upon the size of the patient. Care should be exercised in balloon size selection; too large of a balloon could cause a deep tear into the submucosa, which promotes stricture reformation. After the stricture is dilated, the endoscope must be passed into the stomach to ensure additional esophageal strictures past the one just dilated are not present (especially right at the lower esophageal sphincter). Some cats have more than one stricture, and strictures immediately orad to the lower esophageal stricture may not appear to be a stricture until they are found to impede the advance of the endoscope. Also, looking for potential causes (e.g., hairballs, causes of vomiting) of the esophagitis and stricture is important.

If the stricture is very thin and minimal trauma occurs after it is ruptured (Figure 10-5, *A*), the clinician should recover the patient, send it home, and see if regurgitation recurs in the next 2 to 3 weeks. If the stricture is more extensive, if substantial trauma occurs after dilation (Figure 10-5, *B*), or if the stricture has recurred after prior dilatations, then the clinician should consider placing a gastrostomy tube with the endoscope and dilating the stricture two to three times weekly. The cat should be allowed to eat as soon as it wants to; boluses of food traveling down the esophagus might help it stay open as opposed to allowing it to remain collapsed and reform a stricture. If multiple dilations are required, the idea is to dilate the stricture a little bit each time to keep it from recurring, as opposed to seeing how big you can make it (and thereby causing excessive trauma). Most cats can be cured with one to five dilatations,[22] but occasionally cats may require more than 10 procedures. Finding a stricture without any evidence of active esophagitis seems more favorable prognostically than finding a stricture in association with obvious active esophagitis, but this is anecdotal. Probably more than 85 per cent of the cats with single strictures without concurrent esophagitis are returned to being an acceptable pet, but some must be fed a softened food (not a gruel) for the rest of their lives.

Rarely, the stricture is complete without any lumen detectable (see Figure 10-3, *B*). In such a case, the clinician may advance a stiff guidewire into the center of the stricture and attempt to cause a small perforation in the stricture through which a balloon is inserted. Although the risk is always present that perforation may occur into the pleural cavity, the technique can be successful if performed carefully.

Different clinicians use various modifications in treatment of these patients. Parenteral or intralesional corticosteroids (administered via a needle passed through the endoscopic biopsy channel) have been used in human patients and in some dogs and cats.[23-25] Although use of corticosteroids to slow down stricture reformation makes intuitive sense, no data currently demonstrate their benefit in cats (or dogs). In difficult cases, the clinician may make three or four small, evenly spaced cuts or nicks in the stricture with an electrocautery snare or knife passed through the endoscope immediately before dilatation.[2,24] These nicks are designed to result in a more uniform tearing of the stricture in several spots as opposed to one very deep tear, which extends to the submucosa and is likely to promote restricture. Currently, this procedure probably should be reserved for difficult cases. Treatment for esophagitis (i.e., antacid therapy and gastric prokinetics, with or without a gastrostomy tube) is routine, even if esophagitis was not seen before the dilation. Esophageal dilatation typically is associated with bacteremia in human patients; however, antibiotics generally are not used in cats undergoing this procedure unless a known risk exists of subsequent bacterial infection for that particular patient.

If the clinician elects to use a bougie, the procedure must be done under direct endoscopic or fluoroscopic guidance. Bougies can be passed over a guidewire blindly (not recommended) or beside an endoscope. Pushing the tip of the mechanical dilator against the wall of the esophagus instead of the middle of the stricture is surprisingly easy. In such cases, excessive force can result in esophageal perforation. The clinician should start with a bougie that almost fits through the

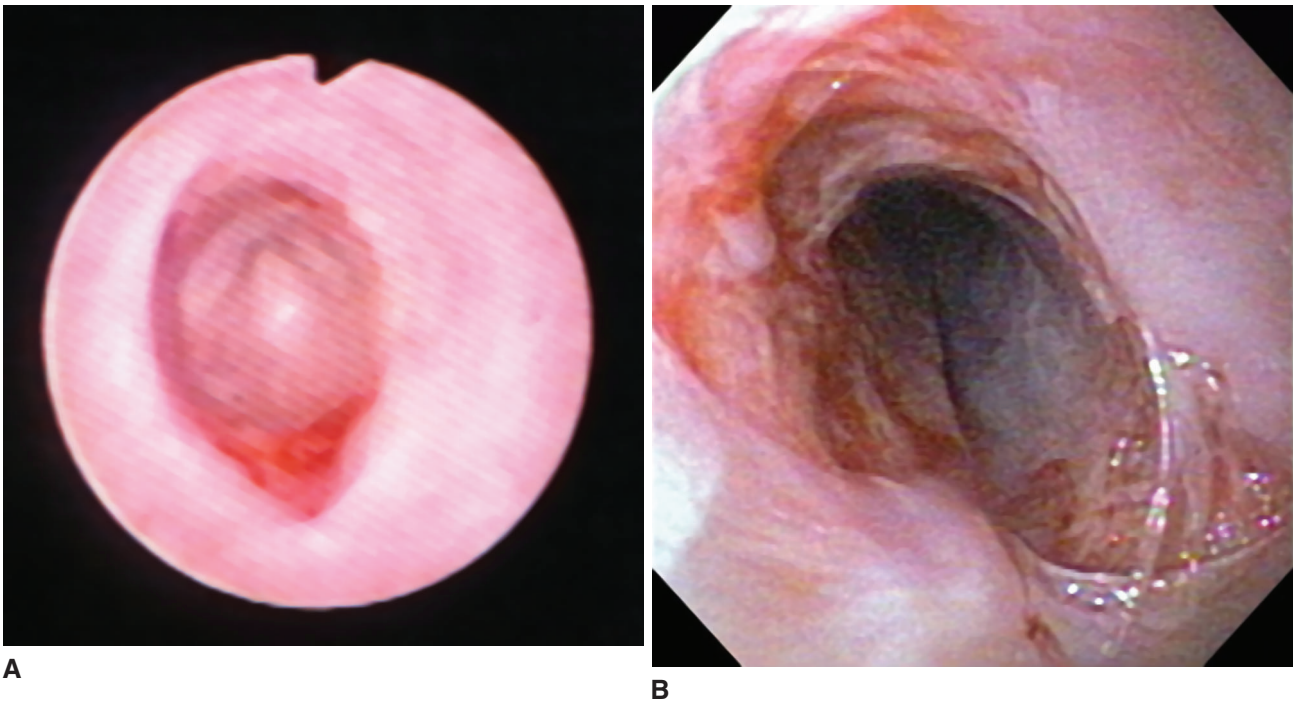


Figure 10-5. A, An endoscopic view of the stricture seen in Figure 10-3, *A,* after it has been dilated once with a balloon catheter. Minimal trauma occurred, and this cat probably will not need additional dilatations. **B,** An endoscopic view of the stricture seen in Figure 10-3, *B,* after it has been dilated once with a balloon catheter. The initial stricture was more extensive than that seen in Figure 10-3, *A,* and correspondingly more trauma exists. Additional dilatations likely will be necessary, although this is not certain.

stricture and then use progressively larger and larger bougies until the desired diameter is reached.

The decision of how much to dilate a stricture with a device is not based on any hard and fast rule. I use the following guidelines. First, causing as little trauma as possible minimizes the chances of restricture. Second, the size of the patient is a consideration in the decision of how much to dilate the stricture. A very small patient typically needs to have relatively more dilation done than a very large patient, simply because large patients may need only 40 per cent (or less) of the potential diameter of their esophagus to allow small food boluses or liquid diets to pass into the stomach. Finally, the goal is to have a functional pet, not necessarily a normal one.

Complications

Major complications associated with dilation of strictures are rare. The most common complication is stricture reformation, and this is almost expected in some cases (i.e., those with severe, long strictures, and those with concurrent esophagitis). The most devastating complications usually involve sepsis, as a result of either aspiration pneumonia or perforation of the esophagus.[22,24] Perforation is a rare event when a trained individual is ballooning a stricture, but it happens occasionally. Inexperienced endoscopists and anyone who balloons a difficult stricture probably should request a thoracic radiograph after the procedure to ensure that no free pleural air or pneumomediastinum exist, signs of probable perforation. If a minor perforation is present, surgery is not always necessary. If a gastrostomy tube is in place, waiting to determine if a minor perforation will heal spontaneously may be reasonable. Fever and dyspnea may be indications that surgery is indicated.

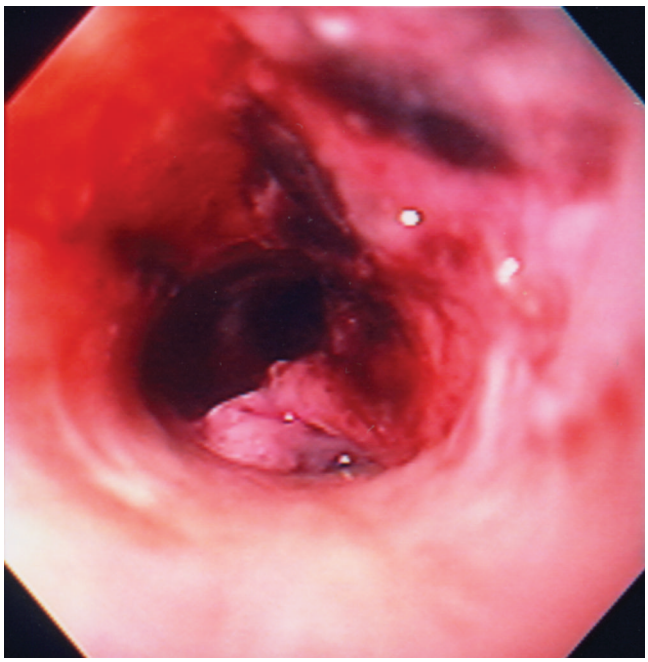


Figure 10-6. An endoscopic view of a large hematoma that occurred after balloon dilatation of a stricture in a cat. The cat became anemic but did not require surgery or transfusion.

Excessive bleeding after dilatation is rare. I have seen only one cat that bled excessively and became anemic (Figure 10-6).[1] Checking coagulation function routinely before ballooning does not seem necessary, because this complication apparently is due to trauma instead of coagulopathy.

If dilatation fails, surgery may be attempted or a stent or permanent gastrostomy feeding tube may be placed.[2] Surgical resection and anastomosis of the esophagus should be performed only by trained surgeons. This can be a difficult procedure, and dehiscence may be more likely than in small intestinal surgery. Stents have been used in human beings, but dogs and cats have additional challenges, especially the fact that the esophagus changes direction as it goes from the cervical to the thoracic regions. This change in direction of the esophagus is significant because it means that the stent may be more likely to erode through the esophagus and cause perforation. Permanent gastrostomy tube placement may be the best option for the patient with an incurable esophageal stricture.

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Chapter 11

Current Considerations for Evaluating Liver Function

Sharon A. Center

Dependable detection of disorders that alter liver size, perfusion, bile flow, hepatocyte integrity, and synthetic and metabolic functions cannot occur simply with use of routine screening assessments. Accurate appraisals require adjunctive interpretation of physical and historical information with routine "screening" tests, imaging studies, and tests that reflect hepatic functions specifically. Accurate diagnostic evaluation of the hepatobiliary system is essential, because this prioritizes acquisition of a liver biopsy, the standard for definitive diagnosis of liver disease.

Performance of a diagnostic test is represented by calculation of test specificity (SP), sensitivity (SS), and positive and negative predictive values (PV+, PV-) (Table 11-1). Calculations of SP and PV depend on disease prevalence in the studied population and inclusion of patients initially thought to have the disease in question but later proven not to be affected. Consequently, reports of "preliminary studies" of unique "new" tests applied only to a very small number of animals or applied only to healthy animals or to animals with experimentally produced disease must be interpreted cautiously. Rigorous evaluation of tests for hepatobiliary disease requires that a *large* number of spontaneously diseased animals be studied that reasonably represent the spectrum of hepatobiliary disorders encountered in practice, along with patients having disorders confused with hepatobiliary disease. Otherwise test evaluation is directed as a screening test. A diverse population of animals must be studied to ensure that SP and PV are relevant to the clinical population in which the test will be applied. High SP is important for a diagnostic test, because this represents the likelihood of a negative test in patients lacking hepatobiliary disease, which are otherwise hard to discriminate (see Table 11-1).

Theoretically, a "perfect" test for liver disease should (1) have good SS but not detect disease before histologically classifiable lesions are present, (2) be influenced minimally by extrahepatic disorders, (3) be convenient, (4) be safe, (5) be affordable, (6) be easy to interpret, and (7) be easy to assay, such that analyses are (8) widely available with a short turnaround time. These characteristics are important to consider when a new test is introduced, especially if it has not been reviewed rigorously and published in a high-impact scientific journal.

ROUTINE SCREENING TESTS

Hemogram

The hemogram in cats with "clinically significant" liver disease often discloses poikilocytes. This term encompasses erythrocytes with an irregular shape, for example, echinocytes, keratocytes, and acanthocytes. Although the cause of altered red cell morphology remains undetermined, it may reflect altered membrane components (phospholipids, cholesterol).

Chemistry Profile

The cholestatic membrane-affiliated enzymes alkaline phosphatase (ALP) and gamma glutamyltransferase (γGT) are useful for recognizing disorders involving biliary or ductal components (biliary, pancreatic). Compared with dogs with liver disease, feline ALP and γGT increase only modestly and do not reflect drug or glucocorticoid induction. However, evaluation of ALP and γGT activity in cats with a variety of liver disorders demonstrates that comparative interpretation of the fold change (magnitude of increase respective to the high reference range value) of enzyme activity has value in prediction of the type of underlying disorder.[1] Highest tissue concentrations of γGT exist in the kidneys and pancreas relative to the liver; however, sources other than the liver do not contribute to the serum γGT activity in health. Inflammatory disorders involving biliary (cholangitis/cholangiohepatitis syndrome [CCHS], extrahepatic bile duct occlusion [EHBDO], choledochitis) or pancreatic ductal components (pancreatitis) cause high serum γGT and ALP activities. Because of the fused pancreatic and distal common bile duct in cats, pancreatitis usually involves pancreatic and bile duct inflammation. Comparative fold increases in serum ALP and γGT in cats with hepatic lipidosis (HL), CCHS, EHBDO, and pancreatitis are displayed in Figure 11-1. Comparative interpretation of these enzymes in

Table 11-1 | **Parameters Used to Evaluate Performance of a Diagnostic Test**

	DISEASE CONDITION	
TEST RESULT	**LIVER DISEASE**	**NO LIVER DISEASE**
Positive	a	b
Negative	c	d
	SP	b/b & d
	SS	a/a & c
	+PV	a/a & b
	–PV	d/d & c

Specificity (SP): True negative test; % negative tests in animals lacking liver disease.
Sensitivity (SS): True positive test; % positive tests in animals with liver disease.
Positive Predictive Value (+PV): % all positive tests represented by animals with liver disease.
Negative Predictive Value (–PV): % of all negative tests represented by animals lacking liver disease.

Test Efficacy: $\frac{\text{True Positive + True Negative Tests}}{\text{All Tests Conducted}}$

HL assists in recognition of the underlying primary disease causing inappetence or malassimilation; cats with idiopathic HL or primary disorders not involving the liver or pancreas have normal γGT activity. In Figure 11-1, HL cats with fold γGT greater than or equal to ALP had CCHS, EHBDO, or pancreatitis. Comparative interpretation of the transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) does not discriminate among hepatobiliary disorders.

Serum cholesterol concentrations can be helpful in refining differential diagnoses for cats with suspected liver disease and for identifying the underlying cause of HL. High cholesterol concentrations are associated with EHBDO and severe CCHS (sclerosing cholangitis form). The percentages of jaundiced cats with abnormally increased or subnormal cholesterol concentrations are summarized in Figure 11-2. In addition to highlighted disorders, high cholesterol concentrations also develop in cats with diabetes mellitus, pancreatitis, and chronic interstitial nephritis, and low cholesterol concentrations also may develop in cats with portosystemic shunting, bowel malassimilation/malabsorption, and hyperthyroidism.

Reduced hepatic urea synthesis is assumed in cats with HL at the time of initial presentation but only rarely in other acquired feline liver disorders. Recognition of normal, low normal, or subnormal BUN concentrations in HL is common despite dehydration that otherwise would precipitate prerenal azotemia (Figure 11-3). This likely reflects restricted availability of arginine necessary for urea cycle function.

Low albumin concentrations are nonspecific for liver disease because these may reflect chronic liver insufficiency, severe diffuse parenchymal dysfunction (diffuse necrosis/failure), chronic inappetence or starvation, inadequate nutritional support, a negative acute-phase response, extracorporeal wasting (enteric, urinary), or third-space distribution (thoracic, abdominal, interstitial).

Interpretation of bilirubin concentrations and the limited value of bilirubin fractionation are discussed below.

Urinalysis

Detection of bilirubinuria is useful as a screening test for hyperbilirubinemia in cats because urine bilirubin is abnormal at any urine specific gravity in this species. Unfortunately, like bilirubinemia, bilirubinuria reflects both hepatic and nonhepatic causes of increased or mismanaged heme pigment flux. Nonhepatic nonhemolytic processes also can increase urine bilirubin excretion, for example, myoglobinemia, enhanced cytochrome turnover, and enhanced enteric bacterial deconjugation of bilirubin pigments. Determining the cause of bilirubinuria requires concurrent evaluation of the hemogram and biochemical profile and in some cases ultrasonographic abdominal imaging.

Interpreting the importance of a urobilinogen test (presence or absence of urobilinogen) requires concurrent evaluation of the serum bilirubin concentration and other biochemical parameters (enzymes, cholesterol). In some cases this also requires abdominal ultrasonographic imaging. In jaundice, the absence of urobilinogen suggests impaired enterohepatic bilirubin circulation as imposed by EHBDO. Unfortunately, extracorporeal influences can reduce urine urobilinogen concentrations (e.g., exposure to light, prolonged urine storage, acidic urine pH). Furthermore, the presence of dilute urine, deranged enteric bacterial flora (response to antibiotics or bowel overgrowth impairing urobilinogen formation), intestinal malabsorption, and decreased intestinal transit time (diarrhea) also can diminish urine urobilinogen concentrations. Detection of ammonium biurate crystalluria strongly suggests the presence of hyperammonemia. This usually is observed in cats with congenital portosystemic vascular anomalies (PSVA) or those with acquired portosystemic shunts (liver diseases causing portal hypertension such as cirrhosis, advanced polycystic liver disease).

Coagulation Tests

The liver plays a central role in coagulation homeostasis. As the single site of synthesis for the majority of coagulation proteins, the liver also synthesizes and/or regulates anticoagulant and fibrinolytic proteins/proteases. The prothrombin complex factors, factors II, VII, IX, and X and protein C and S, depend on availability and activity of vitamin K (fat-soluble vitamin) for normal activation. Active forms of these factors contain carboxylated glutamic acid residues dependent on vitamin K (Figure 11-4). These carboxyglutamate residues bind calcium essential for their adherence to phospholipid-rich surfaces (platelets, collagen). The lack of vitamin K or its functional form impairs normal carboxylation of these factors, which causes the accumulation of nonfunctional precursor proteins. These nonfunctional factors are found in plasma and reflect insufficient vitamin K activation or availability and are referred to collectively as "proteins induced by vitamin K absence or antagonism" (PIVKAs). Prothrombin formed in the absence of vitamin K is not converted to thrombin, which disables both sides of the coagulation cascade at the common pathway. The PIVKA clotting test,* a modified prothrombin time (PT) test, reflects what is thought to be a stoichiometric interference in clot formation by PIVKA proteins. This test is exceedingly

* Thrombotest, Nycomed, Oslo, Norway.

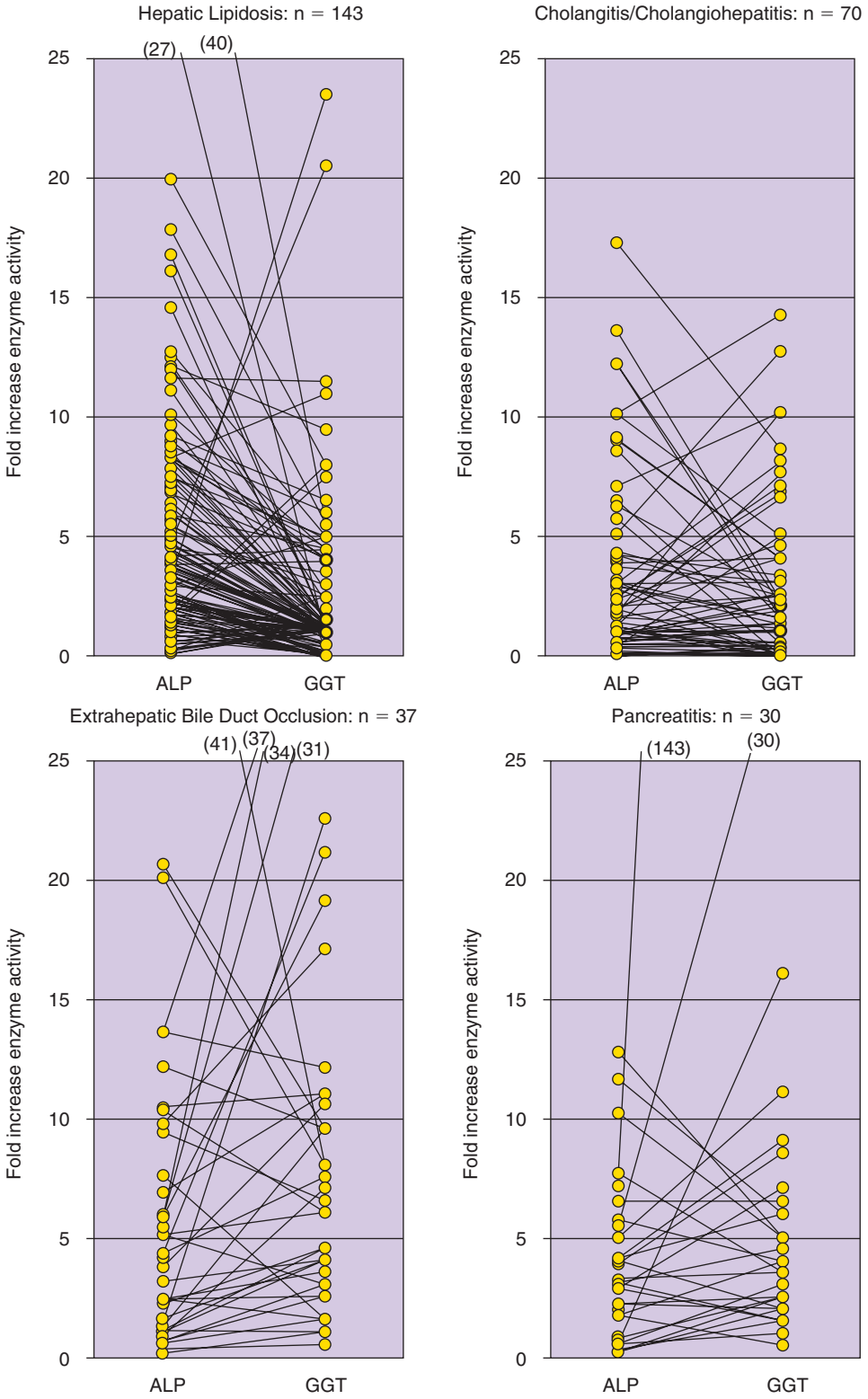

Figure 11-1. Fold increase in serum ALP and γGT activity in cats with hepatic lipidosis, cholangitis/cholangiohepatitis, extrahepatic bile duct obstruction, and pancreatitis. (Courtesy College of Veterinary Medicine, Cornell University, Ithaca, NY, 2004.)

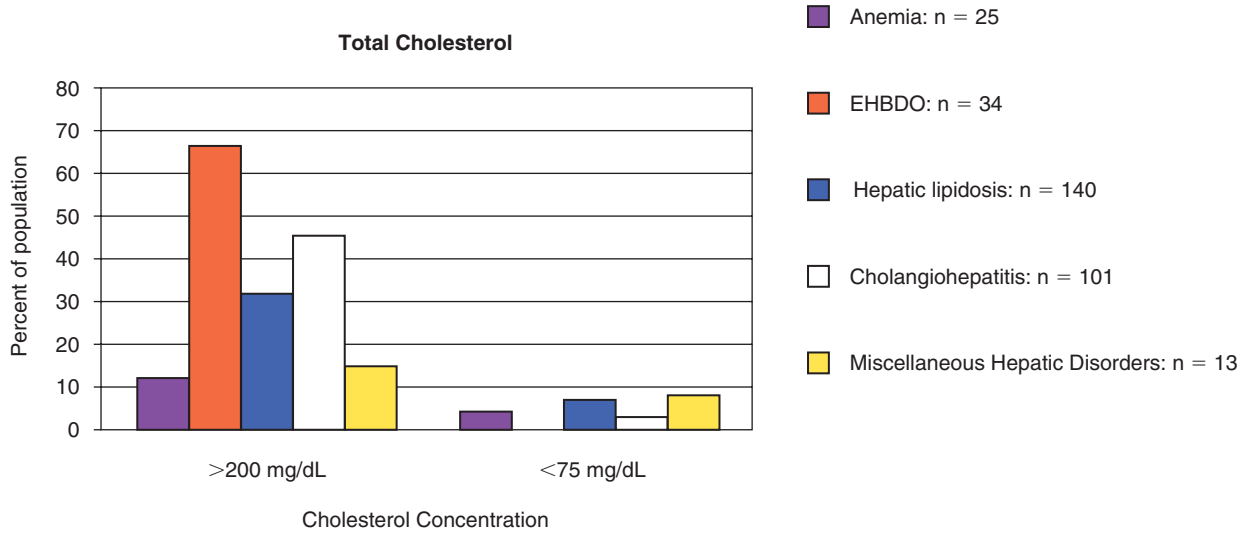

Figure 11-2. Percentage of hyperbilirubinemic cats with hemolytic jaundice and various hepatic disorders with serum cholesterol concentrations above or below the normal reference range. Miscellaneous liver disorders include cats with hepatic lymphosarcoma, hepatic necrosis, hepatic toxoplasmosis, and hepatic jaundice associated with sepsis. (Data derived from the College of Veterinary Medicine, Cornell University, Ithaca, NY, 2004.)

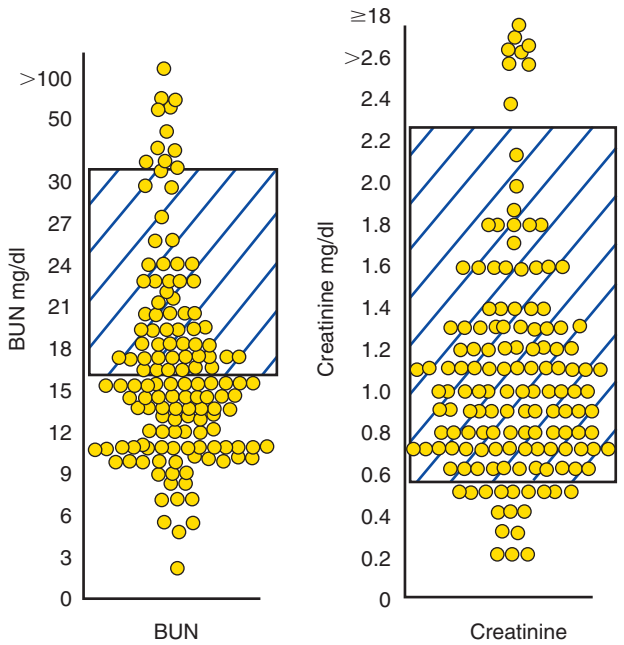

Figure 11-3. Serum BUN and creatinine concentrations in cats with hepatic lipidosis at the time of initial hospital presentation. Note the normal, low normal, or subnormal BUN concentrations in more than 50 per cent of cats despite the common presence of dehydration. Findings support reduced urea formation. (Data derived from the College of Veterinary Medicine, Cornell University, Ithaca, NY, 2004.)

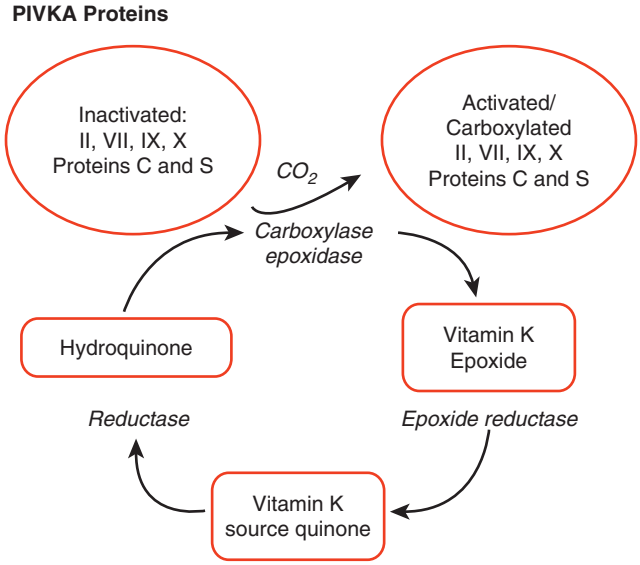

Figure 11-4. Major components of the vitamin K epoxidase cycle.

sensitive for detecting PIVKA factors in citrated plasma from cats with liver disease.[2]

Although vitamin K deficiency is rare in health, its adequacy depends on the diet, intestinal bacterial flora, intestinal absorption, and its rejuvenation in an epoxidase cycle (see Figure 11-4) presumed to predominate in the liver of cats. Deficiency of vitamin K may derive from a number of different clinical circumstances, including dietary restriction of foods containing vitamin K, disruption of enteric bacterial flora normally synthesizing vitamin K (e.g., chronic oral antibiotic administration), fat malabsorption impairing vitamin K uptake from the alimentary canal, ingestion of vitamin K antagonists, or failure of the liver to properly use or restore vitamin K activity after factor carboxylation. Certain antibiotics have been shown to induce vitamin K deficiency directly in human beings and animals, for example, β-lactam second-generation cephalosporins and certain sulfa drugs (sulfaquinoxaline). β-lactam antibiotics may inhibit vitamin K carboxylase, the enzyme involved in factor carboxylation. Sulfaquinoxaline induces hypoprothrombinemia as a result of a synergistic inhibitory effect from the component drug moieties on vitamin K epoxide reductase, which impairs reuse of a single vitamin K molecule in procoagulation activation.

Hemostatic disorders in liver disease are numerous and diverse and may be reflected in a prolonged PT, partial throm-

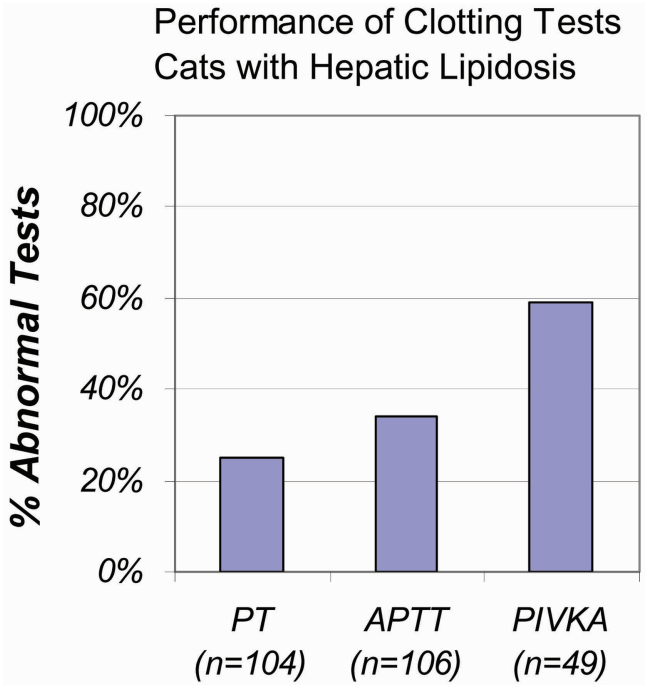

Figure 11-5. Performance of routine bench coagulation tests (*PT,* prothrombin time; *APTT,* activated partial thromboplastin time) and the PIVKA Thrombotest (Thrombotest, Nycomed, Oslo, Norway) in cats with hepatic lipidosis. (Courtesy College of Veterinary Medicine, Cornell University, Ithaca, NY, 2004.)

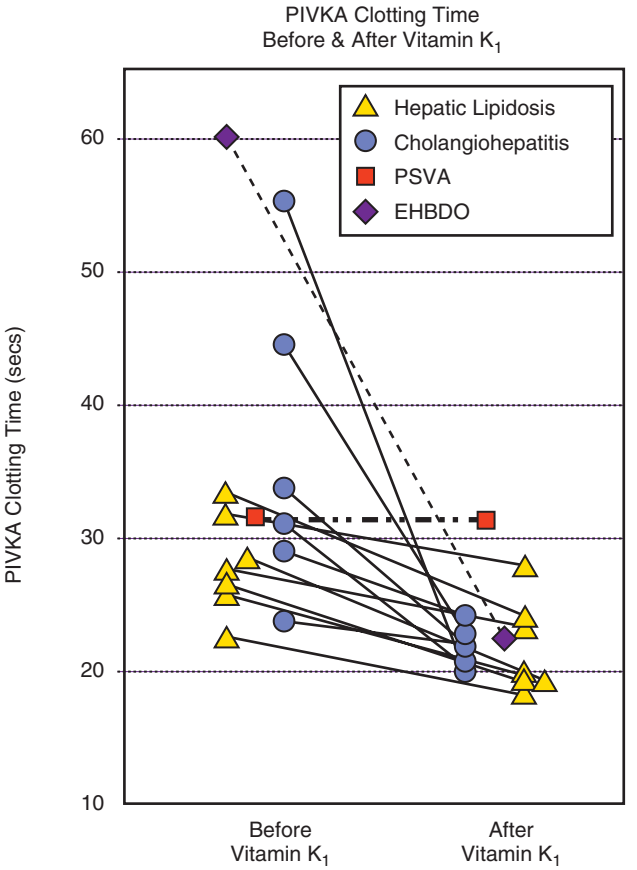

Figure 11-6. The PIVKA Thrombotest (Thrombotest, Nycomed, Oslo, Norway) clotting time before and after parenteral vitamin K_1 (48 to 72 hours, dosing described in text) in cats with various hepatobiliary disorders (*PSVA,* portosystemic vascular anomaly, *EHBDO,* extrahepatic bile duct obstruction). (Courtesy College of Veterinary Medicine, Cornell University, Ithaca, NY, 2004.)

boplastin time (PTT), or the PIVKA time; subnormal fibrinogen concentrations or fibrinogen dysfunction; or increased accumulations of D dimers or fibrin degradation products (FDP). In human beings, hemostatic problems develop in approximately 70 to 85 per cent of patients with confirmed serious liver disease. However, only a small number of these patients develop pathological bleeding. A similar phenomenon also may exist in cats with cholestatic liver disease; comparisons of standard PT and APTT clotting times and PIVKA clotting time are displayed in Figure 11-5 for cats with severe HL. Despite the fact that factor VII (intimately involved in the PT pathway) has the shortest half-life of all the coagulation factors, the standard PT test is not always the dominantly abnormal test. PIVKA clotting times before and after vitamin K_1 administration in cats with different hepatobiliary disorders are displayed in Figure 11-6. Although the PIVKA clotting test appears to be more sensitive for detection of abnormal coagulation compared with coagulation tests routinely used, only a small number of cats with prolonged PIVKA clotting times develop clinical bleeding. Serious hemorrhage seldom develops spontaneously in patients with hepatic disease, even when the liver is severely damaged. In most cases, bleeding develops after venipuncture or at liver biopsy. Spontaneous bleeding usually involves the gastrointestinal tract. In human beings, this is associated with a vasculopathy rather than altered gastrin concentrations. In cats with severe cholestatic liver disease (severe diffuse parenchymal or chronic EHBDO), gastroduodenal ulceration is most common.

All cats with serious liver disease should remain suspects for hemorrhagic complications irrespective of their coagulation profiles. The tenuous balance of the coagulation system in severe liver disease can be upset by a procedure that initiates only small amounts of bleeding and can escalate into critical blood loss that requires blood component therapy. In these animals, administration of citrate anticoagulated blood products may induce ionized hypocalcemia, which causes further bleeding tendencies (ionized calcium is necessary for clotting factor activation) until corrected with calcium chloride or calcium gluconate. Reduced citrate metabolism by the diseased liver causes this iatrogenic complication. All jaundiced cats and cats with liver disease thought to have concurrent enteric disease should receive treatment with vitamin K_1 (0.5 to 1.5 mg/kg SQ or IM, three doses q12h) before invasive procedures. In cats with HL, vitamin K_1 treatment should be provided when the syndrome is first considered, before use of the jugular vein for blood collection, intravenous catheter placement, esophagostomy or gastrostomy feeding tube insertion, cystocentesis, and ultrasound-guided liver aspiration sampling.

Dynamic or Metabolic Tests

Knowledge that the liver removes or modifies a large number of substances from the circulation for subsequent metabolism or excretion has led to the development of a number of

"dynamic or metabolic" tests of liver function. These may involve a xenobiotic or a substrate "probe" extracted, metabolized, or eliminated by the liver, and measurement of it or its metabolite(s). A basic principle of such tests is hepatic clearance, which relates to hepatic perfusion and the substrate extraction ratio (E = ratio of difference between inflow and outflow of substrate concentrations in the liver). Using equations, it is possible to distinguish whether a test reflects primarily liver blood flow ("flow limited" = substrates with E>0.7) or hepatic metabolic function ("enzyme-limited" = substrates with E<0.3). However, application of these calculated ratios is complex. In liver disease, E declines because of a number of factors that effectively increase the rate of hepatic plasma flow across the liver (slight increase in cirrhosis, considerable increase in acute liver failure), including reduced accessibility of plasma to liver cells resulting from sinusoidal capillarization or architectural alteration (e.g., regenerative nodule formation or sinusoidal compression secondary to fibrosis or hepatocyte triglyceride expansion as occurs in HL), reduced permeability of the hepatocyte plasma membrane, and development of direct intrahepatic vascular shunts.

A large number of dynamic or metabolic tests have been proposed for species other than the cat. Some of these tests are difficult to interpret as a result of their dependency on specific enzyme pathways influenced by extrahepatic disorders and conditions or drug therapies. These are especially difficult to interpret in dogs because of this species' extraordinary susceptibility to liver enzyme induction (e.g., phenobarbital, glucocorticoids, other steroid hormones, NSAIDs, other medications). Tests fitting the description of dynamic or metabolic tests that have been explored in cats include (1) the plasma clearance of the xenobiotic cholephilic dyes bromosulfophthalein (BSP) and indocyanine green (ICG), (2) the enterohepatic management of endogenous bilirubin, and (3) serum and urine bile acids, and (4) ammonia detoxification (ammonia tolerance testing [ATT], using either a meal or ammonium chloride [NH_4Cl] challenge). With the exclusion of ammonia, each of these substances is a cholephilic organic anion (OA).

Intact Hepatocyte Hypothesis

Although dynamic tests estimate hepatic metabolism or elimination capability, results reflect the concept of "hepatic functional mass" as defined by the "intact hepatocyte hypothesis" in the disease state.[3,4] This hypothesis maintains that hepatocyte function is preserved in chronic liver disease, with diminution in hepatocyte number and development of functional (anatomical and kinetic) shunts that cause "apparent" alterations in liver function. Acquired microcirculatory deviations (direct artery to venous shunting, blood flow through sinusoids with altered endothelial permeability) impair exchange between hepatocytes and blood perfusing the liver. These contribute to liver failure irrespective of the metabolic capacity of individual cells (Figure 11-7). In chronic disease, this is associated with transformation of hepatic sinusoids (normally having discontinuous capillaries with dynamic fenestrae) into continuous capillaries lacking these numerous portals that facilitate ultrafiltrate formation and substrate diffusion into the space of Disse.

Hepatic fibrosis increases the intrahepatic portal venous resistance, increasing portal pressure even at low flow rates; this favors development of acquired extrahepatic (splanchnic) portosystemic shunts. Intrahepatic "microvascular" shunting between portal and hepatic veins is another cause of deviated blood flow. Studies using human cirrhotic liver explants have demonstrated direct throughput of up to 59 per cent of portal blood flow into the hepatic veins.[4] Reduced sinusoidal space in cirrhosis (secondary to fibrosis, collagenization, remodeling) promotes "streaming" of blood into hepatic venules bypassing hepatocytes. The collective changes restrict hepatocyte access to solutes and contribute to liver failure irrespective of the metabolic capacity of individual cells. Therefore single focus on xenobiotic substrate metabolism for estimation of "hepatic metabolic function" may simply reflect restricted access to functional tissue. This concept is supported by many investigations of xenobiotic metabolism studied in human beings with liver disorders and in a variety of animal models of liver disease.

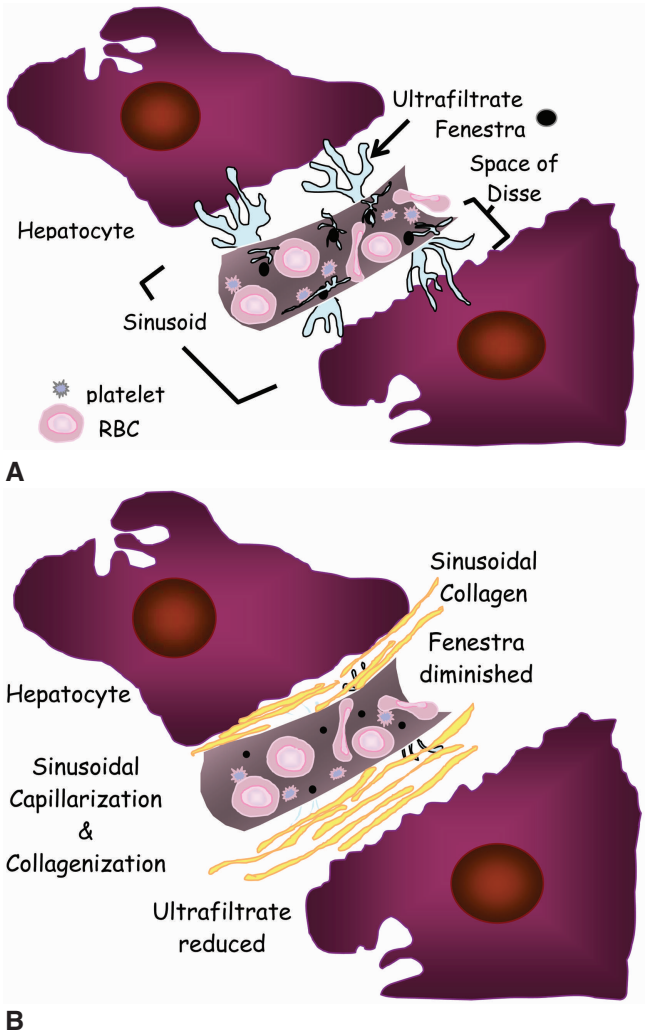

Figure 11-7. Diagram of hepatocytes, hepatic sinusoid, normal discontinuous sinusoidal endothelium with dynamic fenestrae, circulating red blood cells and platelets, and space of Disse in the healthy liver **(A)** and after sinusoidal capillarization and space of Disse collagenization **(B).** Changes indicated in **B** contribute to loss of effective hepatocyte perfusion in acquired liver disease as explained by the "intact hepatocyte hypothesis" described in the text.

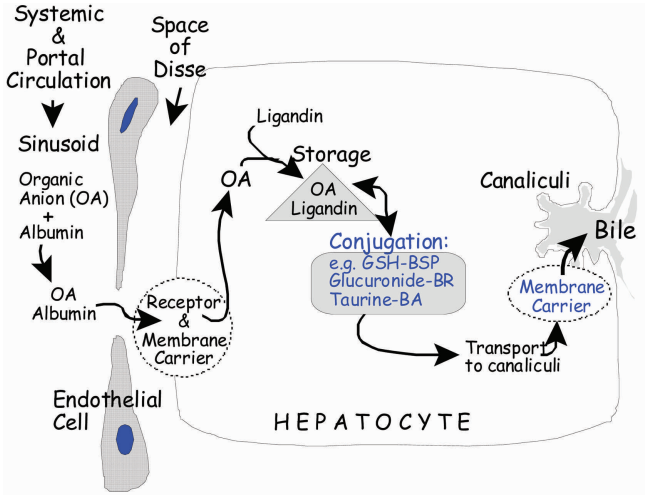

Figure 11-8. Diagram illustrating steps involved in hepatic organic anion (OA) delivery, membrane uptake, cytosolic transport, storage, and metabolism (conjugation for some), and canalicular transport. Any step can influence plasma clearance of the OA. *BA,* Bile acids; *BR,* bilirubin; *BSP,* bromosulfophthalein; *GSH,* glutathione.

Organic Anion Cholephils

OA cholephil uptake and excretion are proposed to provide a sensitive indication of hepatobiliary function and perfusion. Among endogenous OA cholephils are bilirubin and bile acids, proven markers of hepatic disease, cholestasis, and portosystemic shunting (PSS, bile acids only). Among the exogenous OA cholephils are substances used clinically or experimentally to interrogate hepatic blood flow and function and for diagnostic imaging.

The OA cholephils pass into the space of Disse, followed by rapid carrier-mediated uptake across the hepatocellular membranes (Figure 11-8). Competition for hepatic uptake occurs among free and conjugated bilirubin, ICG, and BSP, but not bile acids. Hepatocellular proteins (previously termed ligandin and Y protein, and also identified as involving glutathione [GSH] transferase, GSH peroxidase, and ketosteroid isomerase) transport and store OA in the cytosol of the hepatocyte. For most OA, the maximal hepatocellular uptake exceeds the rate of biliary excretion. Conjugated bilirubin, BSP, ICG, and bile acids occur in bile as mixed micelles or macromolecular aggregates. Although separate biliary secretory mechanisms exist for bile acids and other OAs, these are not fully independent. Any disease impairing biliary excretion promotes OA flux into plasma, thereby increasing their systemic concentrations. Some OAs (BSP, bilirubin, and bile acids) undergo enterohepatic circulation. Deviation of portal splanchnic venous flow to the systemic circulation (portosystemic shunting) causes dynamic and transient increases in the systemic concentrations of cholephilic dyes and bile acids, but does not influence bilirubin concentrations similarly.

Total Bilirubin Concentrations and Bilirubin Fractionation

The serum bilirubin concentration reflects a balance between the rate of heme pigment liberation, its initial processing in the mononuclear/phagocyte system, its presentation to the hepatocyte, and its hepatocellular uptake, storage, conjugation, and biliary excretion. Hyperbilirubinemia associated with hemolysis is termed *prehepatic*, that due to hepatic parenchymal disease or insufficiency is termed *hepatic*, and that due to impaired bile excretion (bile duct occlusion or destruction, or accumulation of bile in the abdominal cavity [bile peritonitis]) is termed *posthepatic*. Unconjugated bilirubin is transformed into conjugated bilirubin by hepatic glucuronide conjugation. Transport of conjugated bilirubin into canaliculi is energy dependent and is the rate-limiting step of bilirubin excretion. When bilirubin has restricted entry into the biliary tract or when excessive liberation of heme pigments overwhelms hepatic capacity for uptake, processing, or excretion, bilirubin regurgitates into the systemic circulation, causing hyperbilirubinemia and jaundice (bilirubin ≥1.5 mg/dL). Because systemic bilirubin concentrations increase only with extensive parenchymal liver disease, this test is relatively insensitive for detection of early diffuse liver disease in dogs. However, because of the cholestatic nature of feline liver disorders, total bilirubin concentrations are more sensitive as a test for liver disease in this species. The total and fractionated bilirubin values and the relative concentrations of each moiety in jaundiced cats are displayed in Figures 11-9 and 11-10.

After conjugation and transport into the biliary system, bilirubin expels with bile into the alimentary canal. Conjugated bilirubin is not absorbed by enterocytes because of its poor lipid solubility. Rather it is excreted in feces or metabolized by colonic bacteria into other products (e.g., urobilinogen may be resorbed and excreted in urine, and stercobilinogens impart a brown/green stool color). The absence of enteric bilirubin, as occurs in complete EHBDO, results in a pale tan or gray "acholic" stool. Acholic feces also may be observed intermittently in cats with severe sclerosing cholangitis. Because even small amounts of enteric bleeding can deliver enough bilirubin to permit formation of stercobilin, finding acholic feces in patients with biliary tree occlusion is inconsistent because of their propensity for hemorrhage (acquired vitamin K_1 insufficiency).

Van den Bergh Bilirubin Fractionation

The total serum bilirubin concentration can be fractionated into unconjugated and conjugated moieties using the van den Bergh reaction; conjugated bilirubin reacts directly (direct bilirubin) and unconjugated bilirubin does not (indirect bilirubin). Although acute hemolytic disorders cause unconjugated bilirubinemia initially, with a normal liver, a rapid rise in conjugated bilirubin soon follows. Canine studies of hemolytic and hepatobiliary jaundice confirm that van den Bergh fractionation has little clinical value.[5] A similar status appears also to hold for cats; see Figures 11-9 and 11-10. Because conjugated bilirubin is less avidly protein bound than the unconjugated form, it is excreted easily by glomerular filtration. However, healthy cats, unlike dogs, do not eliminate bilirubin in urine. Therefore finding bilirubinuria in a cat indicates conjugated hyperbilirubinemia or reduced bilirubin-protein binding (e.g., hypoalbuminemia, displacement of protein binding by exogenous substances [drugs]). In jaundice, formation of covalently bound biliprotein complexes perpetuates systemic retention of bilirubin pigments until the involved proteins are catabolized. Because the percentage of the total bilirubin concentration comprised of biliprotein complexes increases with disease

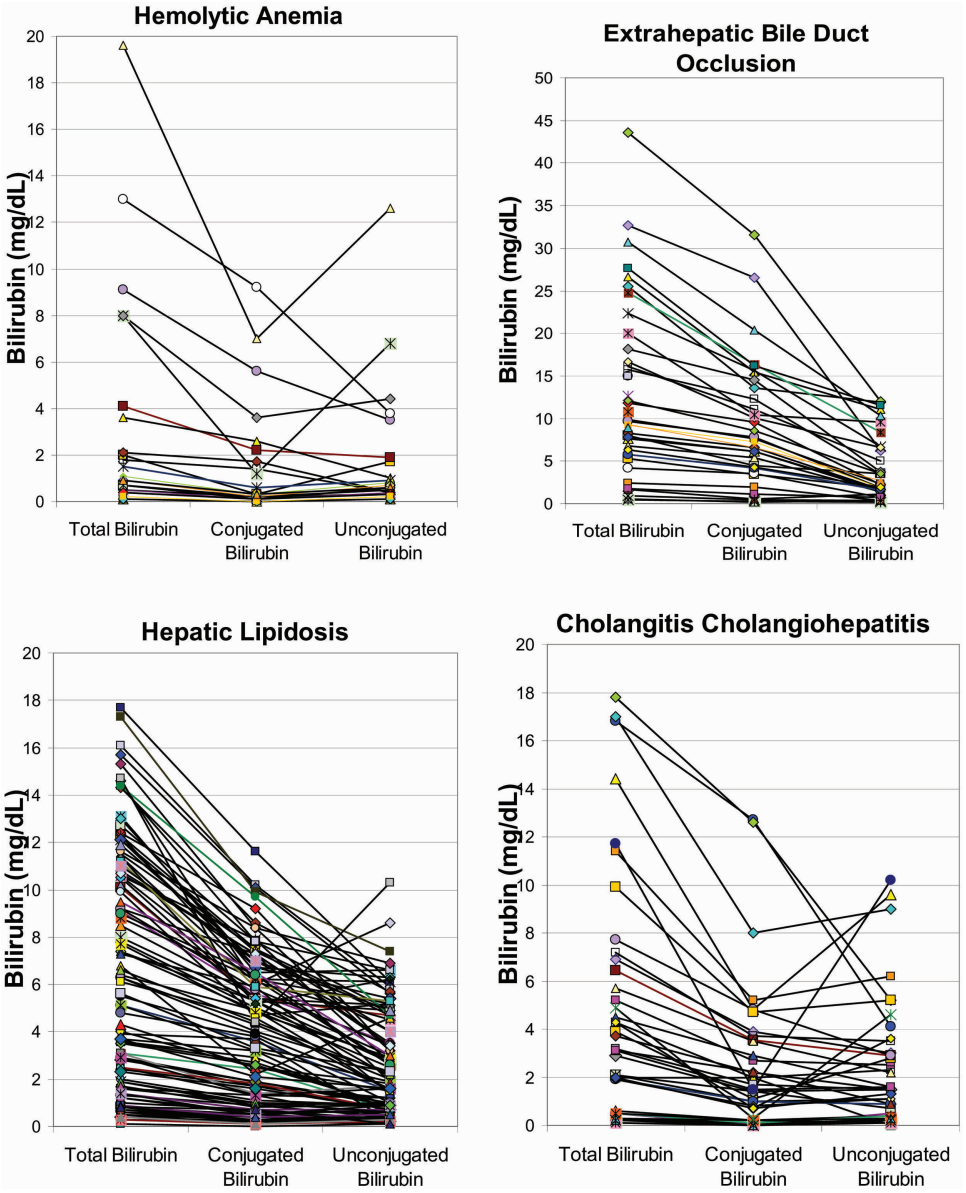

Figure 11-9. Graphs displaying serum concentrations of total bilirubin and the conjugated and unconjugated moieties in hyperbilirubinemic cats with hemolytic anemia, extrahepatic bile duct occlusion, hepatic lipidosis, and cholangitis/cholangiohepatitis. (Courtesy College of Veterinary Medicine, Cornell University, Ithaca, NY, 2004.)

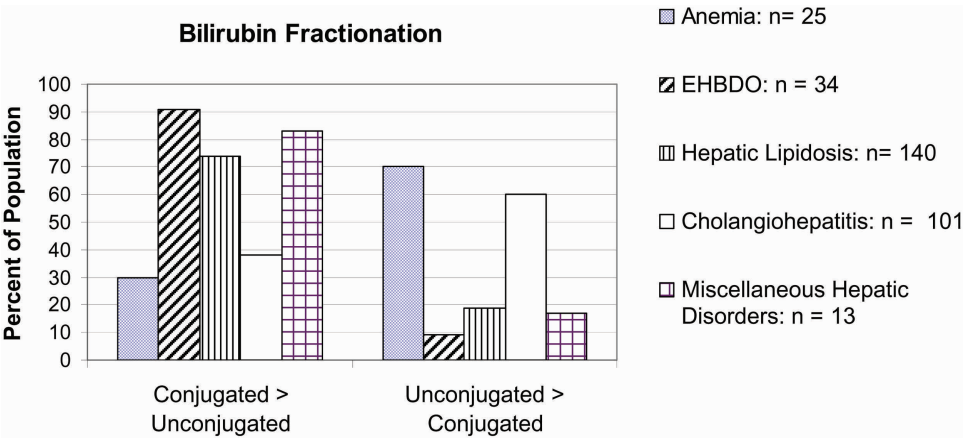

Figure 11-10. Percentage of hyperbilirubinemic cats with hemolytic jaundice and various hepatic disorders with serum conjugated bilirubin greater than unconjugated bilirubin concentration and vice versa. Miscellaneous liver disorders included cats with hepatic lymphosarcoma, hepatic necrosis, hepatic toxoplasmosis, and hepatic jaundice associated with sepsis. (Courtesy College of Veterinary Medicine, Cornell University, Ithaca, NY, 2004.)

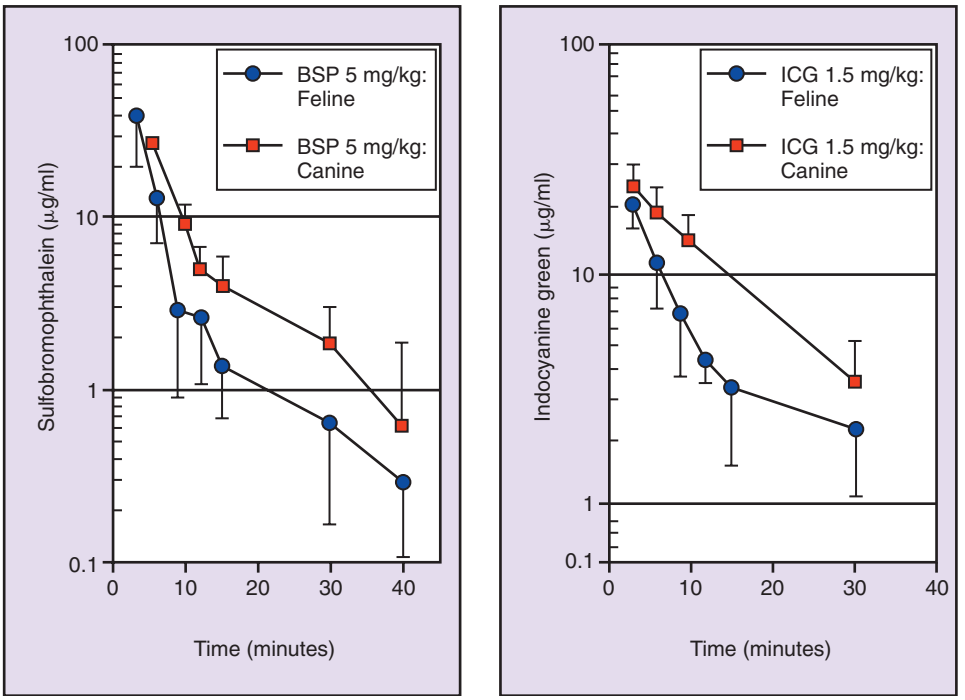

Figure 11-11. Graphs demonstrating plasma clearance (healthy dogs and cats) of bromosulfophthalein (BSP) and indocyanine green (ICG). Note faster clearance rate for cats. (Courtesy College of Veterinary Medicine, Cornell University, Ithaca, NY, 2004.)

chronicity, measurement of the direct-reacting fraction is meaningless unless the biliprotein moieties are quantified concurrently.

A better estimate of the importance of hemolysis in jaundice is accomplished by evaluation of the hematocrit, erythrocyte morphology, serum biochemical profile, and when confusion persists, determination of total serum bile acid (TSBA) concentrations. However, in jaundiced patients with liver disease, measuring TSBA is redundant because the TSBA concentration has higher sensitivity for liver disease and cholestasis than bilirubin.

Although less sensitive than liver enzymes for identifying hepatobiliary disorders, the concentration of total bilirubin is a more specific indicator. Interpreting bilirubin adjunctively with the serum enzymes improves the diagnostic performance of each test. Hyperbilirubinemia resulting from complete EHBDO develops within several hours; jaundice usually is detected within 2 days; and within 3 to 5 days, bilirubin concentrations may increase tenfold to twentyfold from normal. In severe acute diffuse hepatic necrosis, bilirubin may increase twofold within 1 to 4 days but then usually declines if injury abates and reserve capacity reestablishes normal liver function. Differentiating intrahepatic from extrahepatic cholestasis requires consideration of the complete clinical evaluation; adjunctive test interpretation provides better accuracy than any one test or procedure. Cholangiography has not been useful as a routine test in jaundiced cats, whereas abdominal ultrasonography may provide pivotal structural information (evidence of EHBDO, bile peritonitis, parenchymal disease).

Bromosulfophthalein (BSP), Indocyanine Green (ICG)

The OA noncolloidal water-soluble cholephilic dyes, BSP and ICG, have been used clinically to evaluate hepatic perfusion and function in cats.[6] However, clinical application of these tests has declined during the last decade as a result of severe perivascular inflammation associated with extravasation of BSP during intravenous injection, so-called allergic anaphylactoid responses to BSP in human beings, the inconveniences associated with preparation and measurement of ICG, the necessity for timed sequential blood sample collections, and importantly, because numerous variables influence plasma clearance calculations. Both dyes are high-extraction substances that reflect primarily their rate of circulatory dispersal and delivery to hepatocytes.

Because the hepatobiliary plasma clearance of cholephilic dyes involves a complex series of processes, abnormalities in any step can influence their disappearance. ICG is thought to be a better indicator of hepatic function because of its more avid protein binding, more predictable volume of distribution, restricted extrahepatic removal, and its absence of enterohepatic circulation. Overall, cats clear OA cholephilic dyes faster than dogs (Figure 11-11).[6,7] Although ICG can be useful as a test for liver perfusion and hepatocyte OA management for investigative work with cats, the protocol required for correct application imposes unacceptable stress and blood volume collection for an ill cat. Furthermore, the competition between bilirubin and these cholephilic dyes makes the test redundant in many cats with liver disease.

Blood Ammonia (NH_3)

The liver plays a central role in nitrogen metabolism and ammonia (NH_3) detoxification. Severe liver disease can disturb systemic NH_3 homeostasis by diminishing hepatic urea synthesis. Disorders associated with portosystemic shunting also can thwart normal NH_3 detoxification.[8] Either type of disorder can impose episodic hyperammonemia, especially during the postabsorptive (postprandial) interval.

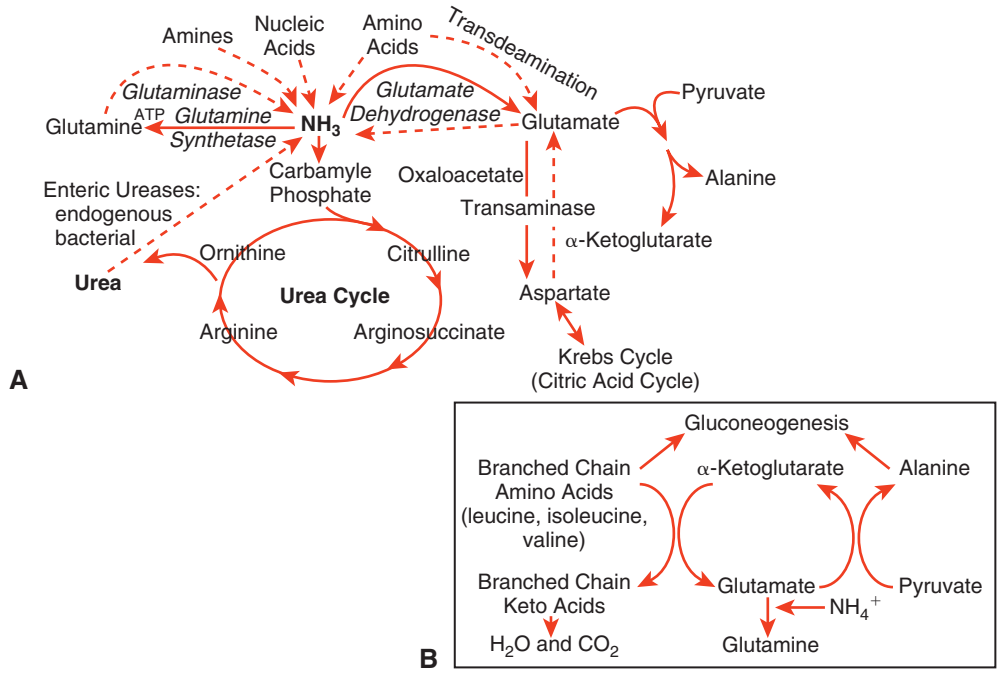

Figure 11-12. Components of the hepatic urea cycle and hepatic glutamine/glutamate transformation that regulate **(A)** ammonia detoxification and **(B)** peripheral production of glutamine (muscle).

Ammonia is produced in the small and large bowel from bacterial breakdown of amino acids and urea. Other systemic NH_3 sources include the skeletal muscles and kidneys, organs involved with flux of NH_3 into and out of the systemic circulation. Skeletal muscle is an important site for temporary storage/utilization and detoxification of NH_3 and may become clinically important in patients prone to hyperammonemia. In muscle, ammonia is *"consumed"* during inosine-monophosphate (IMP) to adenosine monophosphate AMP reamination in the purine nucleotide cycle and also is transitioned into a nontoxic form by synthesis of glutamate, glutamine, and alanine. These amino acids subsequently can be circulated to the liver, kidney, and brain for further metabolism.[9] Glutamine synthesis is an especially important alternative pathway for temporary NH_3 detoxification in muscle. Loss of body condition resulting in reduced muscle mass can impair this important buffering capacity substantially in patients with liver disease. At physiological pH (7.0 to 7.4, in muscle and blood, respectively), muscle contains 2.5 times more NH_3. Synthesis of glutamine (amidation) from equimolar amounts of glutamate and NH_3 is catalyzed by glutamine synthetase. Activity of this enzyme is increased by glucocorticoids, stress, and glutamine depletion.[10]

The kidney removes some systemic NH_3 by excretion of ammonium ions (NH_4^+ acid titration in urine); NH_3 elimination relates to the pH gradient between renal tubular cells and tubular fluid (urine).[11] In the presence of an alkaline urine pH (e.g., subsequent to a metabolic alkalosis and renal compensation), release of NH_3 from the kidneys into blood can increase approximately 2.5 times.[12] Hypokalemia augments renal ammonia flux into the systemic circulation and should be avoided in patients with hyperammonemia.

Hepatic removal and detoxification of NH_3 to urea occurs via a series of enzymatic reactions in the Krebs-Henseleit urea cycle and, to a small extent, by metabolism to glutamine (Figure 11-12). Urea cycle substrate limitations may restrict activity of this important pathway to only a fraction of its theoretical maximum. A special predisposition for substrate restriction exists in the domestic cat in which arginine is an essential amino acid. Nitrogen challenge in healthy cats, in the absence of supplemental arginine, can provoke symptomatic hyperammonemia.[13,14]

Ammonia has long been implicated in the pathogenesis of hepatic encephalopathy (HE) and thus has been suggested to be a relevant test for detection and staging of severe liver dysfunction. However, because HE is associated inconsistently with high blood NH_3 concentrations, its use for monitoring these patients cannot be recommended.[15] The increased susceptibility to hyperammonemia in patients with hepatic insufficiency or portosystemic shunting makes them susceptible to provocative circumstances challenging nitrogen detoxification (Table 11-2).

The exact mechanism(s) through which NH_3 promotes HE are not fully clarified. However, several facts are indisputable: (1) most importantly, NH_3 is proven to impart a direct influence on neuronal function at the cellular level; (2) NH_3 directly promotes γ-aminobutyric (GABA) acidergic neurotransmission; (3) NH_3 upregulates peripheral benzodiazepine receptors thereby augmenting enhanced GABA neurotransmission; (4) NH_3 impairs energy production and increases free radical generation in astrocytes; and (5) NH_3 induces swelling of astrocytes in association with intracellular glutamine, lactate, and alanine accumulation.

Gaseous or free nonionized NH_3 is lipophilic, easily crossing the blood-brain barrier; normally (physiological pH) only 1 per cent of NH_3 is nonionized. Even small changes in pH can shift NH_3 distribution between tissues and blood; nonionized NH_3 at pH values of 6, 7, 8, and 9 approximate 0.1, 1, 10, and 50 per cent of the total (nonionized and ionized) ammonia,

Table 11-2 | **Pathological Conditions Associated with Hyperammonemia**

Hepatic encephalopathy: syndrome indicating hepatic insufficiency or portosystemic shunting
Acquired portosystemic collateral splanchnic shunting: with or without liver disease
Congenital portosystemic shunting: portosystemic vascular anomalies, hepatic arteriovenous fistula
Diffuse hepatocellular failure/necrosis/cirrhosis: acquired, many causes

Conditions provoking hyperammonemia in hepatic insufficiency/portosystemic shunting
- *Constipation:* ↑ NH_3 formation and enteric uptake
- *Enteric nitrogen load:* High-protein diet, enteric hemorrhage: ↑ NH_3 formation
- *Blood transfusion/hemolysis:* ↑ NH_3 formation
- *Dehydration*: Prerenal azotemia ↑ nitrogen challenge
- *Azotemia or uremia:* ↑ Nitrogen challenge
- *Hypokalemia:* ↑ Renal tubular NH_3 production
- *Hypoglycemia*: ↑ Catabolism branched chain amino acids, ↓ cerebral energy, augmented HE toxins
- *Catabolism:* ↓ Muscle mass impairs temporary NH_3 storage and detoxification
- *Sepsis, hypoxia, hypotension*: ↓ Detoxification, ↓ hepatic function
- *Rhabdomyolysis/muscle crush injury:* ↑ Release nitrogenous substrates (glutamine, NH_3)
- *Extreme exercise:* Release of glutamine, NH_3
- *Hepatotoxicity:* Idiosyncratic drug toxicity, i.e., diazepam fulminant hepatic necrosis
- *Enteric bacterial overgrowth:* ↑ NH_3 formation and enteric uptake
- *Urinary tract infection:* Inflammation, ↑ NH_3 formation (urease producing bacteria)
- *Uroabdomen:* With or without infection: ↑ NH_3 formation (+/– urease producing bacteria)
- *Altered peripheral circulation (cirrhosis)*: Vasodilation, ↑ peripheral blood flow, influences peripheral NH_3 uptake, distribution, removal
- *Drugs:* e.g., diuretics (inhibiting liver mitochondrial carbonic anhydrase ↓ urea synthesis; dehydration). Tranquilizers: augment HE neurotransmission (benzodiazepines), others

respectively.[15] Distribution of NH_3 from blood to tissues has been shown to change respectively, at pH values as low as 7.28 and 7.12, or as high as 7.70 and 7.75. Although relatively unexplored in animals, human beings with hepatic insufficiency (cirrhosis) commonly demonstrate a metabolic alkalosis (associated with hypoproteinemia [low albumin concentration] and potassium wasting) that facilitates NH_3 diffusion into the central nervous system.

Hepatic disorders affiliated with hyperammonemia (human beings and dogs) usually are associated with intrahepatic or extrahepatic portosystemic shunting. These are characterized by parenchymal fibrosis, sinusoidal capillarization and collagenization, hepatic and portal venous hypertension, and acquired portosystemic splanchnic shunting. Disorders with similar features are comparatively less common in domestic pet cats. It remains unclear how many feline liver patients develop disease-related hyperammonemia because of unreliable testing methodologies and the feline propensity for NH_3 intolerance.

An ammonia tolerance test (ATT) was investigated in a small number of cats (n = 7) with experimentally induced HL at baseline (obese condition, fasted), and at 2, 4, and 6 weeks of self-imposed starvation (Figure 11-13).[16] Although fasted blood NH_3 concentrations were not substantially different between baseline and HL induction, significant increases in blood NH_3 concentrations developed subsequent to ATT at all tested intervals (sampled 30 minutes after gavage administration of NH_4Cl, dose = 100 mg/kg, solution = 50 mg/ml). Finding abnormal NH_3 tolerance in fasted healthy cats contrasts with the response of similarly fasted healthy dogs and reflects the essentiality of arginine in cats for urea cycle function. Cats are unable to synthesize sufficient arginine from ornithine or citrulline and may become hyperammonemic upon challenge

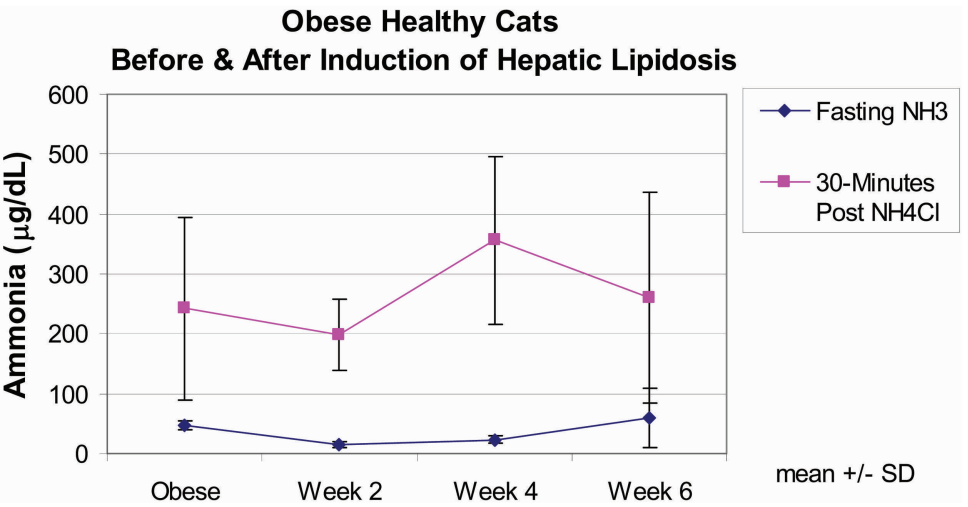

Figure 11-13. Ammonia tolerance test in obese healthy cats and after induced hepatic lipidosis.[17]

with an arginine-deficient high protein or nitrogen load (including NH_4Cl). Feline arginine requirements are not blunted significantly during starvation because of the inability of cats to down-regulate protein metabolism.[13] Findings in the cited study substantiate that ATT testing with NH_4Cl is inappropriate in fasted cats and may be hazardous in ill cats.

High blood NH_3 concentrations are often but inconsistently associated with NH_4-biurate crystalluria. Finding these crystals in the urine of cats with acquired liver disease is exceedingly uncommon, which suggests that hyperammonemia is relatively uncommon. However, NH_4-biurate crystalluria is recognized routinely in cats with congenital or acquired portosystemic shunts, in which related cystic and renal calculi also may develop.

Blood NH_3 measurements impose several obstacles. In human beings, the most common reasons for an abnormally increased blood NH_3 concentration are a poorly taken or processed sample or unstable analytic methodology.[17] Enzymatic assays used currently in most laboratories have undesirable interassay reproducibility. These procedures typically involve two steps: the first liberates blood-bound NH_3, and the second involves its quantification. At least five different methods for the first step and 15 for the second step have been defined through the years.[19]

Most enzymatic methods are based on the following or a similar enzymatic reaction:

$$NH_4^+ + \alpha\text{-ketoglutarate} + NADP \xrightarrow{\text{Glutamate dehydrogenase}} \text{L-glutamate} + NADP^+ + H_2O$$

Blood samples for NH_3 analysis must be collected from a stasis-free vein into an EDTA vacutainer, placed immediately in a melting ice bath, transported promptly to the laboratory, cells removed by refrigerated centrifugation within 15 minutes, and analyzed promptly. Hemolyzed samples must not be used because these may increase plasma NH_3 concentrations spuriously. Blood cannot be preserved at room temperature, especially when collected from a patient with high serum γGT activity. These may undergo rapid enzymatic hydrolysis of glutamine and peptides in plasma, leading to artifactually increased NH_3 concentrations.[20] Delay in analyses can influence ammonia measurements (increasing or decreasing values), although studies with feline plasma indicate less variability than shown with canine plasma (Figure 11-14).[21] Mailing feline plasma for NH_3 analysis cannot be endorsed.

Although performing an ATT with an NH_4Cl solution is contraindicated in inappetent cats or cats suspected of having liver disease, a physiological ATT may be completed by comparison of fasted and postprandial NH_3 values after a balanced feline ration is fed. Using this strategy, hyperammonemia was detected in 81 per cent (9/11) of dogs with PSVA after a 12-hour fast and in 91 per cent (10/11) at 6 hours after eating (chicken and rice [25 per cent of daily metabolizable energy

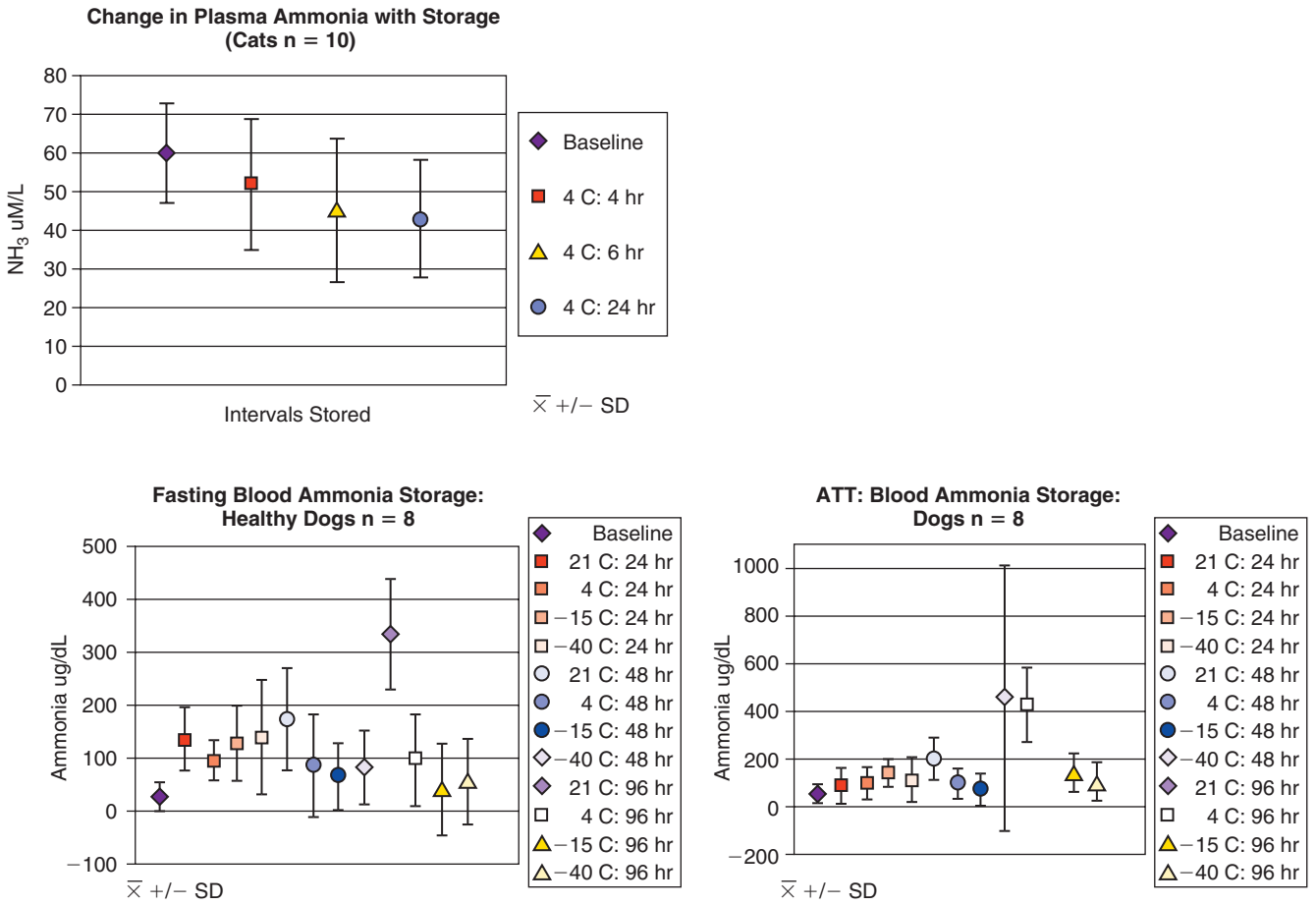

Figure 11-14. Influence of storage (temperature and duration) on ammonia concentrations in feline and canine plasma. (Feline data derived from College of Veterinary Medicine, Cornell University, Ithaca, NY, 2004; canine data from reference 27.)

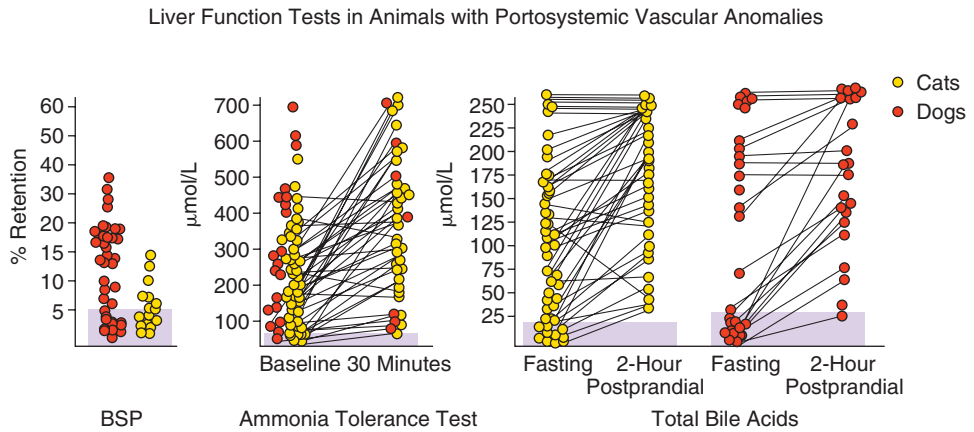

Figure 11-15. Tests of hepatic function in dogs and cats with portosystemic vascular anomalies: bromosulfophthalein (BSP) 30-minute percentage retention, blood ammonia concentrations (fasting and after ammonia tolerance testing with ammonium chloride, see text), and serum total bile acids concentrations (12-hour fasting, 2-hour postprandial). Note the comparable performance of bile acids and ammonia for this disorder. (Data derived from the College of Veterinary Medicine, Cornell University, Ithaca, NY, 2004.)

requirement, 30.3 per cent protein dry matter] was fed).[22] Exactly what postprandial interval would be optimal for detecting NH_3 intolerance in meal-fed cats remains undetermined.

NH_3 is unreliable as a marker of the severity of a patient's clinical signs or stage of disease; spuriously increased values occur. However, because it is unlikely that a blood NH_3 value would be aberrantly low, a normal value can eliminate hyperammonemia as a likely differential diagnosis, although it cannot rule out the presence of HE definitively. No measurement of NH_3 provides dependable evidence of HE, and this test should not be used as the basis upon which to recommend clinical management strategies.

Because paired TSBA concentrations have an equivalent or greater sensitivity than blood NH_3 concentrations in nonjaundiced cats with portosystemic shunting (PSVA patients), the TSBA test is preferred (Figure 11-15).[23] Having broader sensitivity for different forms of liver disease and because bile acids are stable in plasma permitting routine laboratory analysis, the TSBA has displaced NH_3 appropriately as a principal test for hepatic insufficiency. Measurement of blood NH_3 concentrations has been shown repeatedly to have poor sensitivity in detection of liver disease in dogs not associated with hepatofugal circulation (portosystemic shunting); a similar poor sensitivity appears to exist in cats.

Total Serum Bile Acids

Bile acids are OAs with serum concentration dependent on hepatic synthesis, extraction, biliary excretion, passive and active enteric uptake, and integrity of the portal circulation (Figure 11-16). The enterohepatic management of bile acids does not compete with bilirubin, unlike the cholephilic OA dyes discussed previously. When used adjunctively with routine laboratory assessments, TSBA concentrations improve the diagnostic utility of conventional tests for detecting hepatobiliary disorders.[24,25]

The primary bile acids (cholic and chenodeoxycholic acid) are synthesized in hepatocytes from cholesterol and are transported and secreted subsequently into bile after conjugation (amidation) with taurine or glycine (Figure 11-17). The cat conjugates bile acids obligatorily with taurine.[26] The high capacity for bile acid conjugation by the liver favors a predominance of conjugated moieties in the total bile acid pool and in sera. In health, approximately 500 to 1000 times more conjugated acids than unconjugated bile acids exist in serum, and even the oral administration of unconjugated bile acids does not influence this relationship significantly. The majority of enteric bile acids are reabsorbed actively into the portal circulation at the level of the ileum by a sodium-coupled cotransporter. Conjugation favors enteric bile acid ionization and increased water solubility and confers resistance against enteric precipitation with calcium, passive uptake (ionization and comparably large conjugate size deter passage through enterocyte tight junctions), and digestive enzymes. These effects preserve conjugated bile acids within the enteric lumen, which enables their function for facilitating nutrient digestion and assimilation.

During their enteric residence, bile acids are transformed by bacteria (dehydroxylation [primarily loss of the 7α-hydroxyl group] and deconjugation), producing secondary bile acids (deoxycholate from cholic and lithocholic from chenodeoxycholic) and unconjugated bile acids, respectively. Approximately one third undergo enteric deconjugation, and these impart a protective bacteriostatic effect against small intestinal bacterial overgrowth. Uptake of unconjugated bile acids occurs by passive, nonionic diffusion throughout the bowel, but greater quantities are formed and subsequently absorbed in the more distal regions. Although a case has been made for a relationship between abnormally increased serum unconjugated bile acid concentrations and enteric bacterial overgrowth as a diagnostic test, in dogs this association is inconsistent at best.[27-29] Carrier systems governed by sodium-coupled cotransporters in the basolateral membranes of hepatocytes extract bile acids efficiently from the sinusoidal circulation; conjugated bile acids are handled more efficiently. The bile acid pool size and composition are balanced in response to signals derived from the enterohepatic bile acid circulation, which normally functions at high efficiency (≤5 per cent of the entire bile acid pool is lost in feces each day).

The enterohepatic bile acid circulation (see Figure 11-16 and Table 11-3) involves four discrete circuits that influence the homeostatic balance of the bile acid pool. A *cholehepatic*

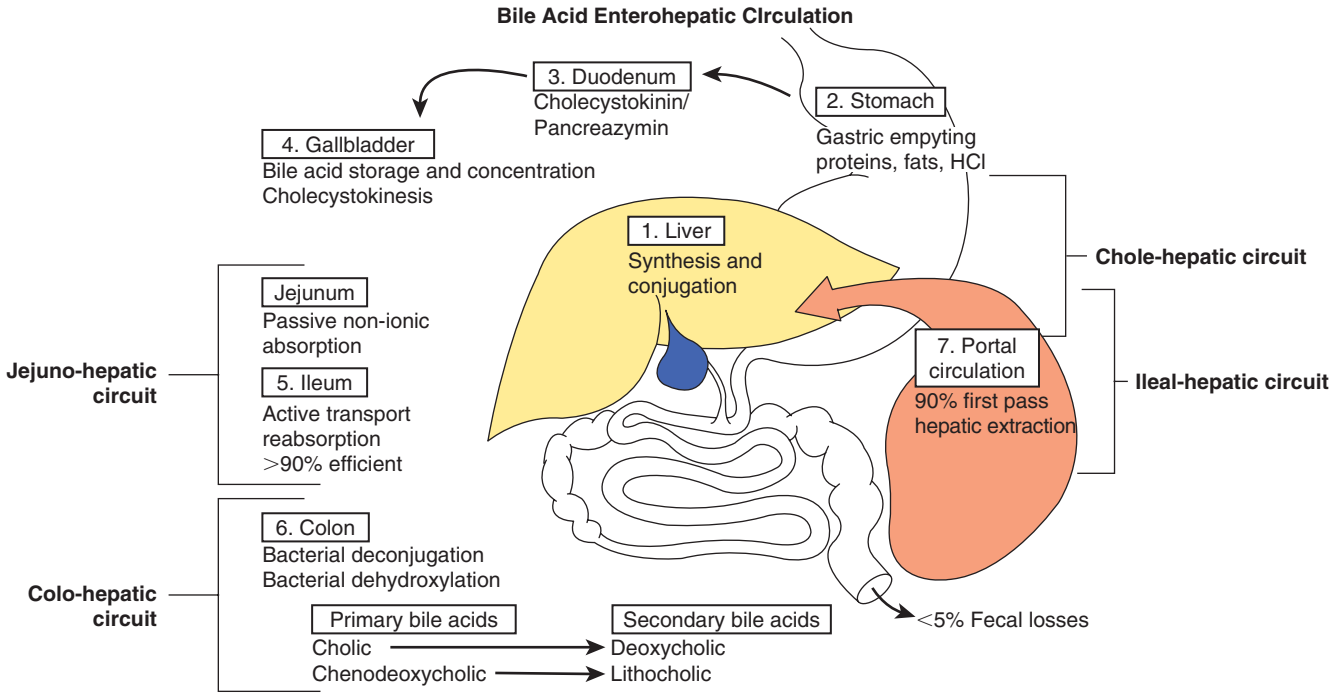

Figure 11-16. Diagram detailing components of the enterohepatic bile acid circulation; individual circuits are discussed in text, numbered references coordinate with Table 11-3.

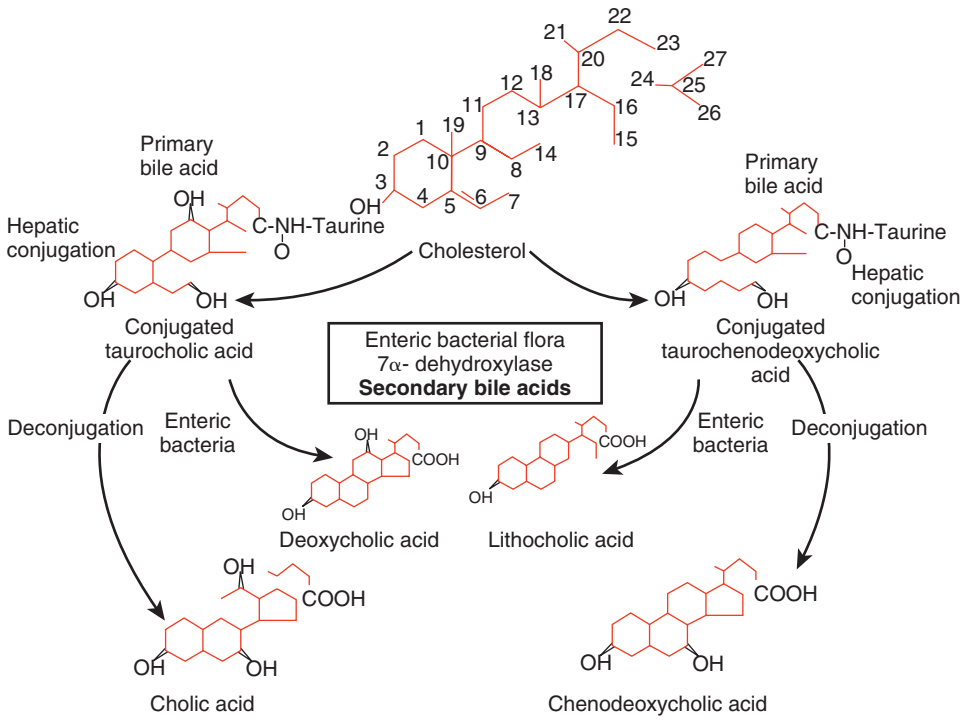

Figure 11-17. Diagram of primary and secondary bile acid structure, conjugation, and enteric modification of bile acids. Note the hydroxyl group in the 3-position (α orientation) that is the basis of the total serum bile acid enzymatic test.

circuit is defined between biliary radicles (canaliculi, bile ductules) and the liver. A *jejunohepatic circuit* is defined for passively absorbed bile acids in the proximal small intestine. This circuit contributes to the increased load of unconjugated bile acids that may reflect enteric bacterial overgrowth in some animals. The *ileal-hepatic circuit* is the major enterohepatic component that influences the TSBA concentrations measured by clinical testing. A *colohepatic circuit* allows for the passive uptake of bile acids that escape absorption in the small bowel or that become unconjugated in the distal alimentary canal; this

Table 11-3 | **Variables Affecting the Serum Bile Acid Tolerance Test***

Impaired hepatic bile acid synthesis: (1)
Not recognized as a test influence; only small quantities of bile acids necessary for test
Hepatic insufficiency/impaired sinusoidal perfusion/intrahepatic shunting: (1)
Compromised hepatocellular bile acid extraction
Contributing conditions: acquired hepatic fibrosis, sinusoidal capillarization and collagenization, regenerative nodule formation, hepatic artery/portal venous shunting to hepatic veins, formation of acquired portal splanchnic collaterals
Cholestatic disease: (1)
Impaired bile acid egress into canaliculi
Impeded bile flow through biliary duct system
Inadequate meal synchronization of enterohepatic bile acid challenge: (2, 3, 4)
Compromised enterohepatic bile acid challenge, fasting bile acids exceed postprandial values
Insufficient food fat/protein, insufficient food intake, gallbladder hypokinesis, abnormal neurohumoral signaling (e.g., CCK release)
Delayed gastric/intestinal transit: (2, 3, 5)
Compromised enterohepatic bile acid challenge within 2-hour test interval
Interdigestive gallbladder
Contraction: (3, 4)
Normal physiological variable; fasting bile acids > postprandial values
Bellows-like interdigestive gallbladder contractions, non–meal-related enteric bile discharge
Rapid intestinal transit: (5, 6)
Reduced intestinal bile acid uptake
Compromised enterohepatic bile acid challenge
Ileal disease or resection: (5)
Reduced bile acid uptake
Compromised enterohepatic bile acid challenge
Small intestinal malassimilation/maldigestion/steatorrhea: (5, 6)
Reduced enteric bile acid uptake
Compromised enterohepatic bile acid challenge
Increased formation of unconjugated bile acids: (5,6)
Small bowel bacterial overgrowth
May contribute to fasting values exceeding postprandial values
Integrity of the hepatoportal circulation: (7)
Reduced hepatoportal circulation: shunting pattern
Numerous causes: congenital or acquired portal systemic shunting, portal venous thromboembolism, portal vein compression/incarceration (neoplasia)

* Refer to Figure 11-16 for numbers in parentheses.

circuit can become important in the circumstance of bile acid malabsorption (e.g., ileal disease or resection).

Bile acid absorption in the colon is influenced greatly by bacterial dehydroxylations forming secondary bile acids; these tend to precipitate and bind with bacteria, which results in low recovery. The physiological mechanisms that maintain adequate bile acid concentrations in the alimentary canal for digestion facilitate the diagnostic value of the TSBA test. Because the bile acid pool recycles multiple times during a single digestive interval, meal ingestion imposes a physiological bile acid flux that challenges the integrity and function of the portal circulation and liver.

All bile acids contain a hydroxyl group at the 3-position on a cholesterol nucleus (see Figure 11-17); it is this bond that is detected sensitively by the standard 3α-hydroxysteroid dehydrogenase (3α-HSD) enzymatic linked assay.[30] This test has been validated carefully, is well described, has been widely applied, is practical, is inexpensive, is safe, has a rapid turnaround time because of its widespread availability, and is reliable for detection of hepatic insufficiency or portosystemic shunting. Using a radioimmunoassay to measure serum bile acids cannot be recommended, because no antibody is capable of detecting the total serum bile acid concentration and no adequate validation of limited bile acid measurements is available.[31]

Although measuring TSBA concentrations in paired samples (fasting, postprandial) has high efficacy, test performance is compromised when only a single random sample is evaluated. In this respect, the TSBA test has been applied inappropriately as a screening test. Finding an increased TSBA concentration with a "random" sample identifies hepatic disease or portosystemic shunting reliably. However, finding a value within the normal range may reflect merely the absence of a provocative enterohepatic bile acid challenge and cannot be relied upon to rule out the presence of liver disease or portosystemic shunting. Understanding the dependency of the TSBA test on the provocative challenge imposed by feeding and survey of at least two paired serum samples is essential for best test application and interpretation (see Table 11-3). In the author's clinic, the "fasted" sample is collected after an overnight fast (9-hour to 12-hour fast) or during an interdigestive interval, followed by meal-feeding (patient's "typical" diet). In cats with suspected HE (neurobehavioral signs), care is taken to avoid feeding a novel or unusually rich high-protein meal. The meal offered should be of sufficient volume (more than a teaspoon) and contain protein and fat to stimulate gastric motility and secretions adequately. These considerations assist in synchronizing enteric motility, cholecystokinin release, bile flow, and gallbladder contraction for optimal testing conditions. The postprandial blood sample is collected 2 hours after verified meal consumption and retention. Although patterns disclosed by paired fasted and fed samples may suggest shunting (Figure 11-18), these patterns are not definitively diagnostic.

Even without gallbladder contraction, substantial amounts of bile bypass the gallbladder, entering the common bile duct and duodenum directly. Bellows-like gallbladder contractions (associated with migrating motor complexes) during the inter-

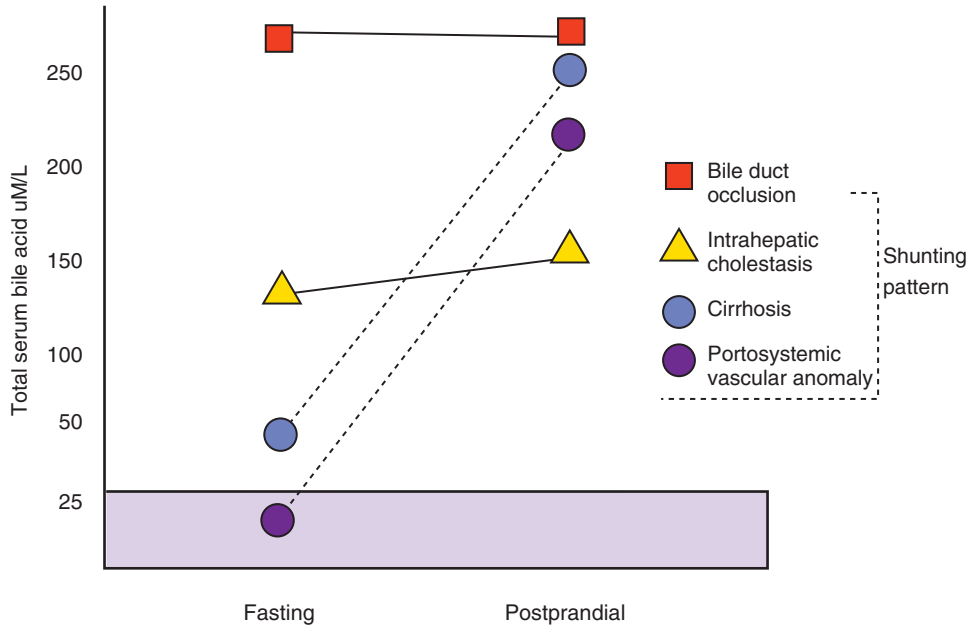

Figure 11-18. General patterns (fasting versus postprandial) of total serum bile acid concentrations. Note the distinct pattern consistent with, but not definitively diagnostic for, portosystemic shunting.

digestive interval facilitate bile discharge into the common bile duct and duodenum and may contribute to the occasionally observed higher fasting than postprandial TSBA concentrations. Intestinal motility may influence bile acid values in several ways; too rapid transit may limit enteric uptake, causing spuriously low values, and hypomotility may delay the bile acid enteric challenge. Compromised intestinal bile acid absorption secondary to severe inflammatory bowel disease or infiltrative lymphoma can thwart accurate testing. Approximately 5 per cent of cats and 20 per cent of dogs demonstrate higher fasting than postprandial TSBA values. This paradox may reflect variations in synchronization of the enterohepatic bile acid challenge and sampling, or less likely, the presence of increased concentrations of unconjugated bile acids. The relative percentage of unconjugated bile acids in the bile acid pool may increase during the late postprandial interval (fasting interval) resulting from their predominant formation in more distal regions of the bowel, their higher rate of passive uptake, and lower rate of hepatic extraction as compared to conjugated forms. Understanding the complexities of the enterohepatic bile acid circulation is essential (see Figure 11-16 and Table 11-3).

Measurement of TSBA by linked enzymatic detection is used routinely in clinical practice.[30] Either serum or heparinized plasma can be used; the latter permits submission of smaller blood volumes and faster sample processing. Available in most veterinary diagnostic laboratories, the test is adapted to automated analyzers. Analytical problems complicating result interpretation involve interference by hemolysis and lipemia in test end-point determination. Hemolysis interferes with testing because hemoglobin shares an absorption spectrum with the test colorimetric end-point. Lipemia can interfere substantially with end-point detection, causing both spuriously high or low values. Lipemia interferes in the following way: bile acid measurement requires splitting a single sample into separate vials; one vial contains 3α-HSD and the other does not. Bile acid concentrations are determined ultimately by end-point color difference between these vials. Differential pipetting of the chylomicron interface can result in different degrees of lipemia in each vial. Lipemia interferes substantially with light dispersal (buoyant fat particles) and can produce either erroneously high or low TSBA readings depending on the degree of lipemia in each vial. To obviate this problem, all lipemic samples must be clarified (chylomicrons removed by sample chilling and high speed centrifugation) before TSBA analysis. Reports detailing sample lipemia and its proposed interference indicate a failure to correct the problem.

Paired TSBA values and the diagnostic performance of the test compared to routine biochemical tests are summarized in Figures 11-19 and 11-20.[25] Although bile acids do not indicate the presence of HE directly as can NH_3, they detect hepatic dysfunction or perfusion abnormalities causing hyperammonemia sensitively (consult postprandial values for PSVA shown in Figures 11-15 and 11-19). Best test utility is achieved with paired fasting and 2-hour postprandial samples.[25] Although some clinicians use the TSBA for serial patient appraisals, there may be limited merit in this practice considering the persistence of chronic architectural and perfusion changes in most acquired disorders. In PSVA, permanent microscopic hepatic vascular malformations may prohibit TSBA normalization after successful surgical ligation. Quantitative association between absolute TSBA concentrations and the "degree," "severity," or nature of liver disease has never been proven (except for the shunting pattern displayed in Figure 11-18). Because marked day-to-day differences in TSBA values can appear within an individual patient, no benefit is gained from a comparison of abnormal values quantitatively in an attempt to judge disease activity or severity. For example, animals with PSVA may have values that vacillate widely between days (e.g., normal values may develop after a prolonged fast to values ≥600 μmol/L), reflecting physiological variations associated with the enterohepatic bile acid circulation. Persistent normalization of previously abnormal values (using paired fasting and postprandial samples) would be the exception (unless an alternative explanation exists, such as enteric bile acid malabsorption).

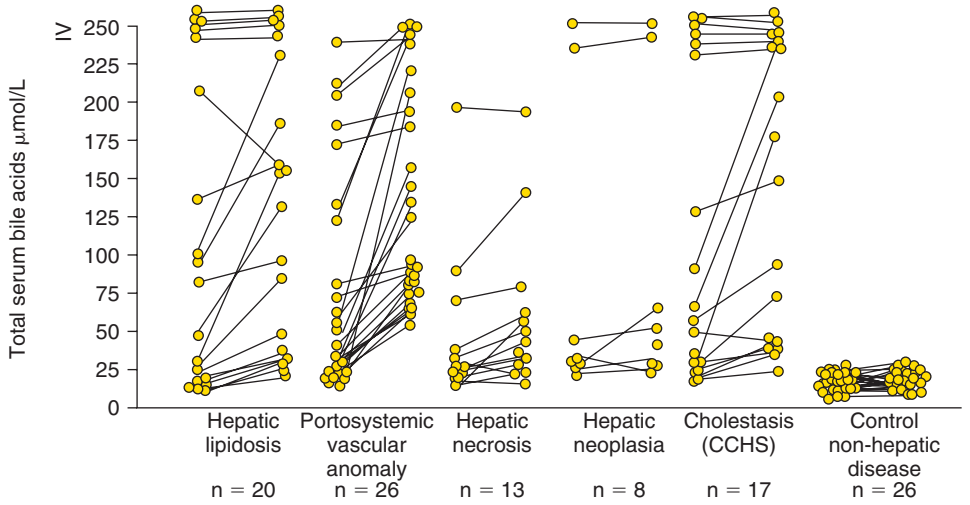

Figure 11-19. Total serum bile acid concentrations (12-hour fasting and 2-hour postprandial) in cats (n = 84) with histologically confirmed hepatobiliary disease, and in cats (n = 26) thought initially to have hepatobiliary disease but proven by liver biopsy not to be affected (control nonhepatic disease group).[25] (Courtesy College of Veterinary Medicine, Cornell University, Ithaca, NY, 2004.)

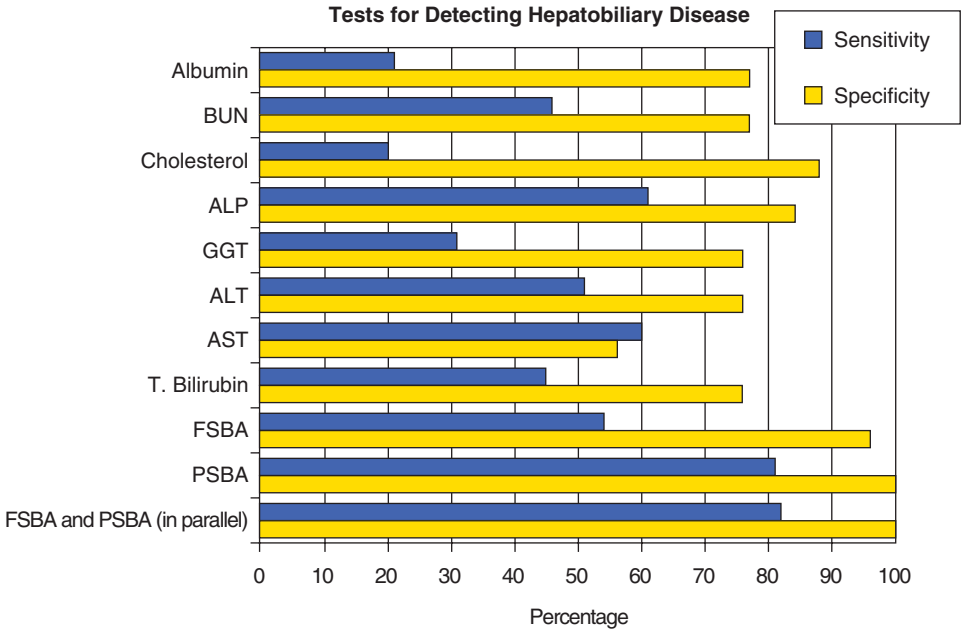

Figure 11-20. Specificity and sensitivity of routine biochemical tests and serum bile acids (12-hour fasting, 2-hour postprandial, and fasting with postprandial in parallel [either test abnormal]); values derived from individuals depicted in Figure 11-19.[25]

The need to withdraw treatment with ursodeoxycholic acid (UDCA) before a TSBA test is conducted is often recommended by diagnostic laboratories. Influence of UDCA (15 mg/kg PO) on serial TSBA concentrations in normal dogs (n = 14) over a 12-hour interval (sampled q2h) confirmed that 40 per cent (6 of 14 dogs) developed abnormally increased TSBA values at the 2- through 6-hour postprandial/post-dosing interval.[32] Although median TSBA values remained within the reference range, higher values developed at all intervals after oral UDCA administration. Significant increases with values exceeding the reference range occurred at the 2-hour, 3-hour, and 4-hour intervals in individual dogs. Erroneous diagnosis of hepatobiliary disease is possible therefore in patients receiving UDCA, based on this work in dogs. These findings are at odds with a recent report of 16 normal dogs administered a comparable UDCA dose for 7 days in which only fasting and 2-hour postprandial TSBA values were measured at baseline and on day 7.[33] Only a single dog developed an abnormally increased TSBA concentration at the 2-hour postprandial interval. Different outcomes may be due to the limited sampling and averaged data in the cited report.

Urine Bile Acids (UBA)

To avoid the shortcomings of collecting only a fasting or random TSBA sample, and interference by hemolysis or lipemia, determination of UBA has been investigated as an alternate approach. Normally, only small amounts of bile acids

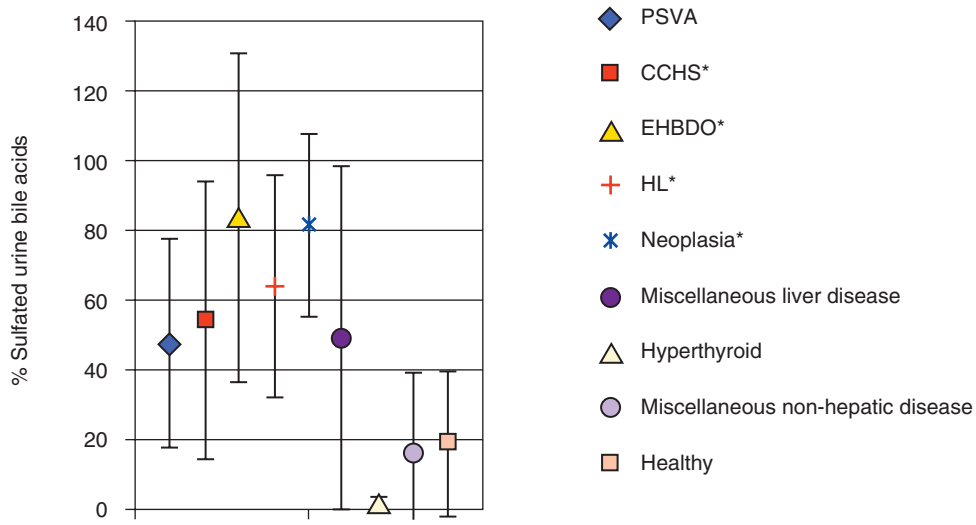

Figure 11-21. Graph displaying the percentage of sulfated urine bile acids (3-position) in healthy cats and cats with liver disease, hyperthyroidism, and ill with miscellaneous nonhepatic disorders.[37]

are eliminated in urine. However, water-soluble conjugated and sulfated forms may appear in urine as an alternative excretory route in human patients with high TSBA concentrations.[34-36] In human beings, sulfate conjugation has been identified as an alternative detoxification method for membranocytolytic bile acids. The extent of urinary elimination of bile acids in cats and dogs has been investigated.[37,38] Healthy cats eliminate, on average, approximately 20 per cent of UBA as sulfated moieties, whereas dogs do not (Figure 11-21).[38] Cats with liver disorders associated with increased TSBA concentrations, especially those with cholestatic disorders, eliminate a significantly greater percentage of sulfated UBA.

A method was developed to measure both sulfated and nonsulfated UBA, so a single assay could be applied to urine from dogs and cats.[37,38] After optimization of a linked enzymatic colorimetric method detecting both sulfated and nonsulfated UBA and validation and recovery studies, two prospective clinical studies investigated UBA in randomly collected urine.[37,38] Test interpretation requires normalization of UBA concentrations with urine creatinine (UCr) concentrations to adjust for variations in urine specific gravity; values are expressed as

$$\text{UBA/Cr } (\mu\text{mol/mg}) \times 100$$

Findings in these studies support that UBA can effectively "screen" for abnormally increased TSBA in either species; UBA/UCr greater than 7.3 are abnormal in dogs, whereas UBA/UCr values greater than 4.4 are abnormal in cats. The lower feline range once again is consistent with the general observation that cats clear OAs faster or more efficiently than dogs. Data in the feline study included serum and urine bile acid values from 54 cats with hepatobiliary disease, 17 cats with nonhepatic disorders, and eight normal cats.[38] Diagnostic performance of the UBA/UCr test rivaled that of the TSBA test: UBA/Cr: SP = 88 per cent, SS = 85 per cent, +PV = 96 per cent, –PV = 65 per cent; TSBA: SP = 88 per cent, SS = 87 per cent, +PV = 96 per cent, –PV = 68 per cent. The UBA/UCr values and corresponding TSBA values (highest value shown for each cat) in cats with different hepatic and nonhepatic disorders and normal cats are shown in Figure 11-22. These studies confirm that the UBA/UCr test is highly correlated with the TSBA test and has surrogate diagnostic value.

Two cats with PSVA tested in the prospective study described had abnormal UBA/UCr values lower in magnitude than anticipated. This observation correlates with a similar trend noted in dogs with PSVA in which randomly collected UBA/UCr values had SS similar to fasting TSBA concentrations. Further investigation of the UBA/UCr test in PSVA has been completed in dogs, in which the disorder is more common.[32] In 71 PSVA dogs, SS of fasting TSBA was 89 per cent, SS of postprandial TSBA was 96 per cent, and SS of random UBA/UCr was 92 per cent. Test efficacy using random UBA/UCr samples in these patients reflects the dynamic and only transiently increased TSBA associated with portosystemic shunting. Investigation of the temporal association between UBA/UCr and meal ingestion in dogs with PSVA (serial urine samples collected before and after feeding, sampled q2h for 12 hours) demonstrated SS was 100 per cent for UBA/UCr at postprandial hours 4 through 8, SS was 73 per cent after an overnight fast, and SS = 80 to 90 per cent at the 1-hour, 2-hour, 3-hour, 10-hour, and 12-hour postprandial intervals.[39] Similarly collected postprandial UBA/UCr values in normal dogs did not exceed the normal reference range established previously. These findings correspond with the expected lag time for high TSBA to appear in urine (urine formation). Subsequently, we recommend collection of urine for UBA/UCr testing at 4 through 8 hours after meal ingestion to optimize test efficacy (comparable with postprandial TSBA).

The advantage of using a UBA/UCr test to estimate liver function includes improved owner convenience and reduced patient stress. Pet owners can feed their cat at home peacefully and nonstressfully, remove litter box access, and present the cat for a 4-hour to 8-hour postprandial urine collection. Some owners are able to collect urine at home. The urine test avoids repeated venipuncture and eliminates the hemolysis, lipemia, and collection of random blood samples that complicate the diagnostic performance of the TSBA test.

Investigation of the influence of oral UDCA (15 mg/kg) on UBA/UCr concentrations in healthy dogs (after an overnight fast and at 2-hour intervals for 12 hours after UDCA dosing at

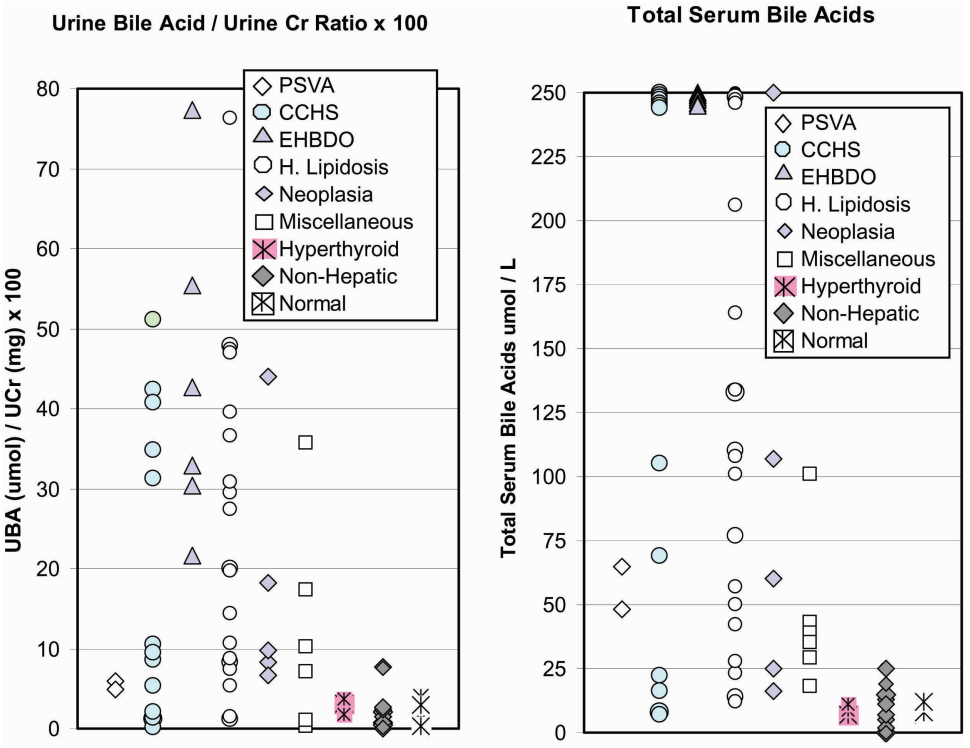

Figure 11-22. Individual urine bile acids (UBA)/urine creatinine (UCr) (µmol/mg ratio × 100) and corresponding total serum bile acid concentrations (highest values shown for each individual using fasting and postprandial values) for cats described in Figure 11-20. Correlation between tests indicates that UBA/UCr can function as a surrogate for testing serum bile acid concentrations.

the time of meal ingestion) demonstrated only a rare influence on UBA/UCr values. Abnormally increased UBA/UCr was identified in only one out of 14 dogs after UDCA administration (4-hour postdosing postprandial interval). This contrasts with the more common influence of UDCA (in healthy dogs) on the TSBA concentrations, described above. These findings suggest that UBA/UCr values may be less influenced by therapeutically administered UDCA. No similar studies have been conducted in cats regarding the influence of UDCA on TSBA or UBA/UCr values.

CONCLUSION

Evaluation of liver function is an evolving science. Many aspects of liver function assessment have been described in this chapter, and each must be integrated with subjective and objective clinical and diagnostic information for best utility. Although the search for improved tests of liver function for cats continues, currently available methods have proven useful and reliable in recognizing disease patterns and in identifying the need for liver biopsy. No test surpasses liver biopsy for definitive diagnosis of hepatobiliary disease. Improved disease surveillance by combined application of routine assessments and the useful liver function tests described here has shortened the interval between disease onset and its definitive histological characterization and treatment.

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Chapter 12

Acute Necrotizing Pancreatitis

Robert J. Washabau

Acute necrotizing pancreatitis is one of many pathologies that involve the feline exocrine pancreas (Figure 12-1). Based on a series of reports over the past decade,[1-11] we now have a much better understanding of the natural history of these diseases. A pathological classification of feline exocrine pancreatic disease has been used to delineate these disorders. However, significant overlap exists between several disease categories, particularly with regard to acute and chronic forms of pancreatitis.

Acute necrotizing pancreatitis (ANP) is a lesion characterized by pancreatic acinar cell and peripancreatic fat necrosis (>50 per cent of the pathology), with varying amounts of inflammation, hemorrhage, mineralization, and fibrosis. Inflammation may be present, but necrosis is the predominant feature. Reports of this condition were uncommon before the early 1990s, probably related to difficulties in diagnosis in addition to lower incidence of disease. ANP is now a well-recognized gastrointestinal disorder of significant morbidity and mortality in domestic cats.[1-10]

Acute suppurative pancreatitis (ASP) differs from ANP in that neutrophilic inflammation accounts for more than 50 per cent of the pancreatic pathology. Necrosis may be present, but neutrophilic inflammation is the predominant feature. ASP is less common than ANP, appears to affect younger animals, and may have a different pathogenesis.[2,5,6,10]

Chronic nonsuppurative pancreatitis (CP) is a lesion characterized by lymphocytic inflammation, fibrosis, and acinar atrophy. Necrosis and suppuration may be present in small amounts, but lymphocyte infiltration is the predominant feature. Antemortem differentiation of CP and ANP cannot be made on the basis of clinical, clinicopathological, or imaging findings[10]; histopathology remains the only dependable method of differentiating these two disorders.[10] CP and ANP may vary in their pathogeneses, or they may represent a continuum of disease from necrosis to inflammation and fibrosis.[1,10]

In *pancreatic nodular hyperplasia*, nodules of pancreatic acinar or duct tissue are distributed throughout the pancreatic parenchyma. Fibrosis, inflammation, necrosis, and hemorrhage are not features of this condition. The clinical significance of this lesion is unknown. Pancreatic nodular hyperplasia often is detected at the time of routine abdominal ultrasonography or as an incidental finding at necropsy. Its ultrasonographic characteristics may be difficult to differentiate from those of ANP.

Pancreatic neoplasia may be primary (e.g., adenoma, adenocarcinoma) or secondary, and they are classified as benign or malignant. Pancreatic adenocarcinoma is the most common malignancy of the feline exocrine pancreas and is of ductal (primarily) or acinar origin. Neoplastic infiltration may be accompanied by necrosis, inflammation, fibrosis, hemorrhage, or mineralization in some instances.

Pancreatic pseudocyst is a common complication of pancreatitis in human beings, and a not-so-common complication in cats and dogs.[12] Pancreatic pseudocyst is a non–epithelial-lined cavitary structure that contains fluid, pancreatic cells, and/or enzyme. It is observed at the time of ultrasound, CT scan, surgery, or necropsy. It is important to differentiate its ultrasonographic characteristics from those of pancreatic abscessation.

Pancreatic abscess is a circumscribed collection of purulent material that involves the right or left lobe of the pancreas. Like pseudocyst, pancreatic abscessation is a complication of pancreatitis in human beings and dogs.[13] The incidence and significance of this lesion in cats are unknown. Medical and surgical therapies have been used to manage pancreatic abscesses in dogs.

Pancreatic atrophy may result from degeneration, involution, necrosis, or apoptosis of the exocrine portion of the gland. Most feline cases are believed to represent the end stage of chronic pancreatitis. The endocrine portion of the gland may or may not be involved in the same process. Exocrine pancreatic

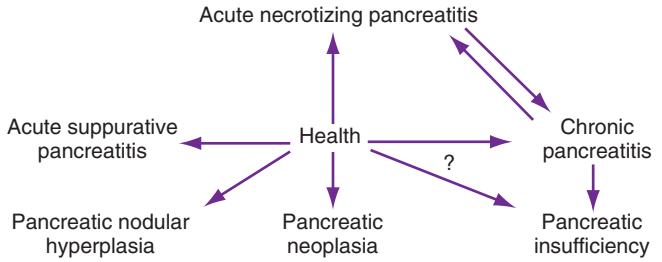

Figure 12-1. Pathogenesis of feline exocrine pancreatic disease.

Table 12-1 | **Etiologies of Feline Acute Necrotizing Pancreatitis**

KNOWN ASSOCIATIONS	
Biliary tract disease	Gastrointestinal disease
Ischemia	Ductal obstruction
Infection	Trauma
Organophosphates	Lipodystrophy
SUGGESTED ASSOCIATIONS	
Hypercalcemia	Drug reactions
Nutrition	

insufficiency is the clinical syndrome that results from 95 per cent or greater loss of exocrine pancreatic function. Affected animals develop a classic maldigestion syndrome characterized by weight loss, steatorrhea, and diarrhea.[11]

ETIOLOGY

The etiologies of ANP probably are not yet recognized completely. Biliary tract disease, gastrointestinal tract disease, ischemia, pancreatic ductal obstruction, infection, trauma, organophosphate poisoning, and lipodystrophy have known associations with the development of ANP in cats. Hypercalcemia, idiosyncratic drug reactions, and nutritional causes are suggested but unproved associations in feline ANP (Table 12-1).

Concurrent Biliary Tract Disease

Concurrent biliary tract disease has a known association with ANP in cats. Cholangitis is the most important type of biliary tract disease for which an association has been made,[14] but other forms of biliary tract pathology (e.g., stricture, neoplasia, and calculus) have known associations.[2,9] Epidemiological studies[14] have shown that cats affected with suppurative cholangitis have significantly increased risk for pancreatitis. The pathogenesis underlying this association is not entirely clear but relates partly to the anatomical and functional relationship between the major pancreatic duct and common bile duct in this species.[15,16] Unlike dogs, the feline pancreaticobiliary sphincter is a common physiological and anatomical channel at the duodenal papilla (Figure 12-2). Mechanical or functional obstruction to this common duct readily permits bile reflux into the pancreatic ductal system. Bile salt perfusion (e.g., 1 to 15 mM sodium cholate or glycodeoxycholate) of the major pancreatic duct induces changes in the permeability of the pancreatic duct,[17,18] and sustained elevations in ductal pressure (>40 cm H_2O) and bacterial infection induce pancreatic acinar

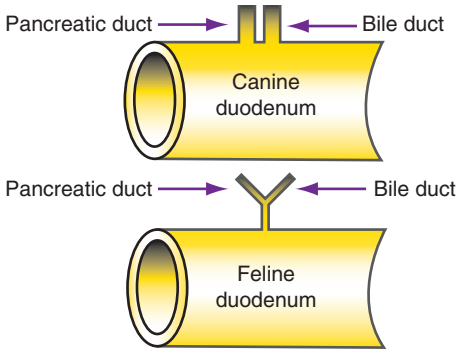

Figure 12-2. Differences in pancreaticobiliary anatomy between cats and dogs. Pancreatic and bile ducts have separate channels of entry in the canine small intestine, whereas these ducts merge before their entry in the feline small intestine.

necrosis.[18] Ductal pressures are increased readily by biliary infection, and ductal compression is a predictable consequence of sustained ductal hypertension and pancreatic interstitial edema.[18,19]

Concurrent Gastrointestinal Tract Disease

Like concurrent biliary tract disease, *inflammatory bowel disease (IBD)* is an important risk factor for the development of ANP in cats.[14,20] Several factors apparently contribute to this association:

1. High incidence of IBD: This is a common disorder in domestic cats.[20-22] In some veterinary hospitals and specialty referral centers, IBD is the most common gastrointestinal disorder in cats.
2. Clinical symptomatology of IBD: Vomiting is the most important clinical sign in cats affected with IBD.[20-22] Chronic vomiting raises intraduodenal pressure and increases the likelihood of pancreaticobiliary reflux.
3. Pancreaticobiliary anatomy: The pancreaticobiliary sphincter is a common physiological and anatomical channel at the duodenal papilla[15,16]; therefore, reflux of duodenal contents would perfuse pancreatic and biliary ductal systems.
4. Intestinal microflora: Compared with dogs, cats have a much higher concentration of aerobic, anaerobic, and total (10^9 vs. 10^4 organisms/ml) bacteria in the proximal small intestine.[23,24] Bacteria proliferate readily in the feline small intestine because of differences in gastrointestinal motility and immunology.[25,26] If chronic vomiting with IBD permits pancreaticobiliary reflux, a duodenal fluid containing a mixed population of bacteria, bile salts, and activated pancreatic enzyme would perfuse the pancreatic and biliary ductal systems.[27]

Ischemia

Ischemia (e.g., hypotension, cardiac disease) is a cause or consequence of obstructive pancreatitis in cats. Inflammation and edema reduce the elasticity and distensibility of the pancreas during secretory stimulation. Sustained inflammation increases pancreatic interstitial and ductal pressure, which

further reduces pancreatic blood flow, organ pH, and tissue viability.[28-30] Acidic metabolites accumulate within the pancreas because of impaired blood flow.[30-32] Ductal decompression has been shown to restore pancreatic blood flow, tissue pH, and acinar cell function.[31,32]

Pancreatic Ductal Obstruction

Pancreatic ductal obstruction (e.g., neoplasia, pancreatic flukes, calculi, and duodenal foreign bodies) is associated with the development of ANP in some cases.[9,33] Pancreatic ductal obstruction has marked effects on pancreatic acinar cell function. During ductal obstruction, ductal pressure exceeds exocytosis pressure and causes pancreatic lysosomal hydrolases to co-localize with digestive enzyme zymogens within the acinar cell.[34] Co-localization is the underlying pathogenesis for digestive enzyme activation within the acinar cell because lysosomal enzymes (e.g., cathepsin B) activate trypsin readily.[34]

Infection

Infectious agents have been implicated in the pathogenesis of feline ANP, although none have been reported as important causes of ANP in any of the recent clinical case series.[1-10] The pancreas is colonized readily by *Toxoplasma gondii* organisms during the acute phase of *infection*.[35] In one survey of *T. gondii*–infected cats, organisms were found in the pancreas of 84 per cent of the cases, although pathology was more severe in other organ systems.[35] *Feline herpesvirus I* and feline infectious peritonitis viruses have been implicated as causative agents in several case reports,[36] and feline parvoviral infection has been associated with viral inclusion bodies and pancreatic acinar cell necrosis in young kittens.[37] Pancreatic (*Eurytrema procyonis*) and liver fluke (*Amphimerus pseudofelineus*, *Opisthorchis felineus*) infections are known causes of ANP in cats in the southeastern United States and Caribbean Basin.[33,38] Recent outbreaks of virulent caliciviral infections have been reported in multiple-cat households or research facilities (see Chapter 1). Affected cats manifest high fever, anorexia, labored respirations, oral ulceration, facial and limb edema, icterus, and severe pancreatitis.[39-41] Caliciviral infection has not been reported in any of the recent clinical case series of feline ANP[1-10]; however, some cases of active infection could have been overlooked. The importance of calicivirus infection in the pathogenesis of feline ANP is not yet determined.

Trauma

Trauma in the form of automobile and fall ("high rise syndrome") injuries has been associated with the development of ANP in a small number of cases.[42,43] These tend to be isolated cases that do not show up as important causes in clinical case surveys.

Organophosphate Poisoning

Organophosphate poisoning is a known cause of ANP in human beings and dogs,[44] and several cases have been reported in cats.[2] In one survey, several cats developed ANP after treatment for ectoparasites, and two cats developed ANP after treatment with fenthion.[2] Diminishing organophosphate usage probably will lead to a reduced incidence of this lesion.

Lipodystrophy

Lipodystrophy has been cited as an occasional cause of ANP in cats,[45] but it has not been reported in any of the large clinical case series.

Hypercalcemia

ANP develops in association with the *hypercalcemia* of primary hyperparathyroidism and humoral hypercalcemia of malignancy in human beings, and a weak association with hypercalcemia has been reported in dogs.[12] Moderate hypercalcemia was found as a preexisting laboratory finding in 10 per cent of the cases of fatal canine acute pancreatitis.[12] Acute experimental hypercalcemia does indeed cause ANP in cats,[46,47] but probably it is not clinically relevant. Acute hypercalcemia is an uncommon clinical finding in feline practice. Chronic hypercalcemia, a more clinically relevant condition, is not associated with changes in pancreatic morphology or function[48] (see Chapter 17).

Idiosyncratic Drug Reactions

Idiosyncratic reactions with azathioprine, L-asparaginase, potassium bromide, and trimethoprim sulfa have been reported in association with the development of ANP in dogs.[12,49] Similar associations have not been made in cats. Glucocorticoid administration has been suggested as a cause of acute pancreatitis in dogs, but a firm association has not been confirmed in either species. Indeed, antiinflammatory doses of glucocorticoids apparently are beneficial in the management of experimental canine ANP.[50]

Nutrition

High-fat feedings[51] and obesity[49] have been associated with the development of pancreatitis in dogs, but similar associations have not been made in cats. Most recent surveys have associated underweight body condition with the development of feline ANP.[2,6,8,10]

PATHOGENESIS

The acinar and ductal cells of the exocrine pancreas are interspersed between the islet cells of the endocrine pancreas. Like the endocrine pancreas, the exocrine pancreas is a secretory organ with several physiological functions. Exocrine pancreatic fluid contains digestive zymogens that initiate protein, carbohydrate, and lipid digestion; bicarbonate and water, which neutralize the duodenum; intrinsic factor, which facilitates cobalamin (vitamin B_{12}) absorption in the distal ileum (see Chapter 13); and antibacterial proteins, which regulate the small intestinal bacterial flora. Acinar cells primarily secrete digestive zymogens, whereas ductal cells primarily secrete bicarbonate, water, intrinsic factor, and antibacterial proteins. The two most common disorders of the exocrine pancreas, acute pancreatic necrosis and exocrine pancreatic insufficiency, are readily understood on the basis of these physiological functions. With acute pancreatic necrosis, premature activation of

digestive zymogen within pancreatic acinar cells leads to acinar cell necrosis (trypsin, chymotrypsin, carboxypeptidase), hemorrhage (elastase digestion of blood vessel elastin fibers), and fat necrosis and saponification (lipase digestion of pancreatic, peripancreatic, and mesenteric fat). With exocrine pancreatic insufficiency, affected animals develop severe nutrient maldigestion, acid injury to the duodenal mucosa, cobalamin and fat-soluble vitamin malabsorption, and bacterial proliferation in the gut.[52]

Pancreatic acinar cells protect themselves from intraacinar activation of zymogen and acinar cell necrosis through several mechanisms: (1) Potentially harmful digestive enzymes are synthesized in the form of inactive precursors or zymogens in the rough endoplasmic reticulum. (2) Zymogens are then transported to the Golgi complex, where they undergo selective glycosylations. Lysosomal hydrolases that are packaged eventually in lysosomes are separated from zymogens bound for export as they pass through the Golgi complex. Lysosomal hydrolases are first phosphorylated at the 6th carbon position of mannose residues, bound to receptors specific for 6-phosphoryl mannose, and then transported to lysosomes where the acid pH favors their dissociation from the receptors. Digestive enzymes lack the 6-phosphoryl mannose label and instead are transported vectorially into a different secretory fraction. (3) Packaging of zymogens into maturing zymogen granules sequesters them from contact with other subcellular fractions. (4) Pancreatic secretory trypsin inhibitor (PSTI) is incorporated into the maturing zymogen granules. PSTI inactivates trypsin should there be any intraacinar activation of trypsinogen. (5) After stimulation (e.g., feeding and cholecystokinin secretion), mature zymogen granules and their contents are released from the cell into the ductal lumen in a process of membrane fusion and exocytosis. (6) Finally, zymogens are activated physiologically only after they enter the duodenum, where the brush border enzyme enteropeptidase activates trypsinogen, and trypsin then activates other pancreatic zymogen (Figure 12-3).[52]

A large body of experimental, and some clinical, evidence suggests that the initiating event of acute pancreatitis is the premature activation of digestive zymogens within the acinar cell.[34,53-56] Premature activation of digestive zymogen results in acinar cell necrosis and pancreatic autodigestion. In acute pancreatic necrosis, protein synthesis and intracellular transport to the Golgi complex appear to be normal, but digestive zymogens then become co-localized along with lysosomal hydrolases in large vacuoles. Cell biology studies have revealed that lysosomal and zymogen granule fractions become co-localized through a process known as crinophagy, a process used by many cells to degrade accumulated secretory products when the need for secretion no longer is present. Although this process takes place in other cells without adverse consequences, it can be lethal in pancreatic acinar cells because of the peculiarity of their secretion products (digestive zymogens). Lysosomal hydrolases, such as cathepsin B and N-acetyl glucosaminidase, activate trypsinogen to the active trypsin form, and the enhanced fragility of these large vacuoles permits release of active enzyme into the cell cytoplasm (Figure 12-4). Trypsin acts autocatalytically to activate other trypsinogen molecules and other zymogens; each induces a unique chemical pathology in pancreatic and extrapancreatic cells. A variety of inflammatory mediators and cytokines, interleukins, nitric oxide, and free radicals are involved in the further evolution of pancreatic acinar cell necrosis and inflammation and often determine the outcome.[52,57-60] Therefore, a bout of pancreatitis begins with an *initiating event* (e.g., ischemia, inflammation, or ductal obstruction), followed by *acinar events* (i.e., co-localization, enzyme activation, and cell injury), the outcome of which is influenced by *severity determinants* (e.g., inflammatory cytokines, reactive oxygen species, altered redox state, and apoptosis) (Figure 12-5).[59] The further evolution of ANP to a systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction

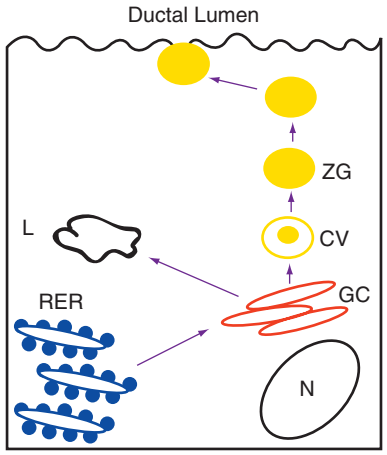

Figure 12-3. Intracellular trafficking of zymogens and lysosomal hydrolases in pancreatic acinar cells. Digestive zymogens and lysosomal hydrolases are synthesized on the rough endoplasmic reticulum *(RER)* and transported to the Golgi complex *(GC),* where they undergo selective glycosylation. Lysosomal hydrolases are phosphorylated at 6-mannose residues and transported to lysosomes *(L)* via receptors specific for 6-phosphoryl mannose. Digestive enzymes lack the 6-phosphoryl mannose label and instead are transported vectorially into condensing vacuoles *(CV).* Condensing vacuoles mature into zymogen granules *(ZG)* whose contents are released into the pancreatic ductal system following feeding. Trypsinogen is converted to active trypsin by intestinal enterokinase, and inactive zymogens are converted to active enzymes by tryptic hydrolysis. *N,* Nucleus. (Modified from Steer ML, Meldolesi J: The cell biology of experimental pancreatitis. N Engl J Med 316:144-150, 1987.)

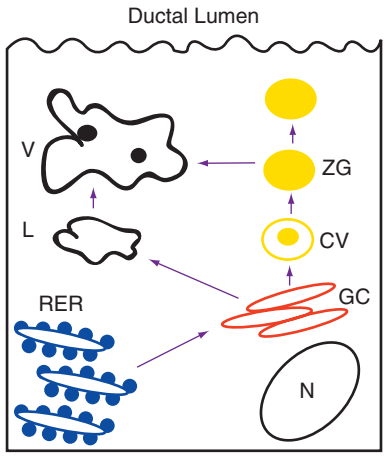

Figure 12-4. Cell biology of pancreatic acinar cell necrosis. Pancreatic enzyme secretion is inhibited and pancreatic zymogens become co-localized with lysosomal hydrolases within large vacuoles *(V).* Lysosomal hydrolases activate digestive zymogens prematurely within pancreatic acinar cells. (Modified from Steer ML, Meldolesi J: The cell biology of experimental pancreatitis. N Engl J Med 316:144-150, 1987.)

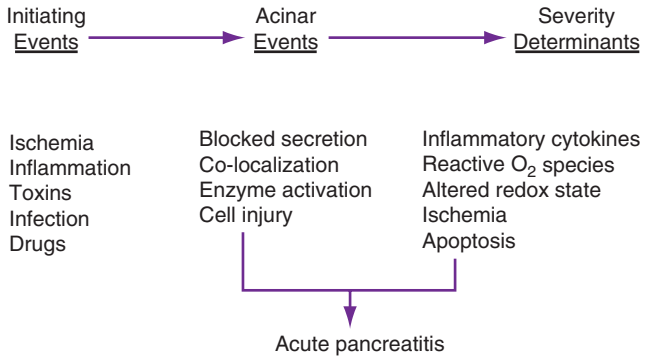

Figure 12-5. The three phases of acute pancreatitis. Pancreatic necrosis begins with an initiating event (e.g., ischemia, inflammation, or ductal obstruction), followed by acinar events (e.g., co-localization, enzyme activation, and cell injury), the outcome of which is influenced by severity determinants (e.g., inflammatory cytokines, oxygen free radicals, ischemia, and apoptosis). (Modified from Steer ML: The early intra-acinar cell events which occur during acute pancreatitis. Pancreas 17:31-37, 1998.)

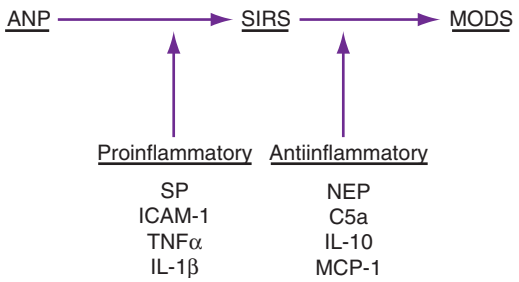

Figure 12-6. Final evolution of acute necrotizing pancreatitis. Severe cases of ANP may progress to a systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). The balance between proinflammatory and antiinflammatory molecules determines the outcome. *SP,* Substance P; *ICAM-1,* intercellular adhesion molecule-1; *TNFα,* tumor necrosis factor α; *IL-1β,* interleukin-1β; *NEP,* neutral endopeptidase; *C5a,* complement factor 5a; *IL-10,* interleukin-10; *MCP-1,* monocytic chemotactic factor-1. (Modified from Bhatia M, Brady M, Shokuhi S, et al: Inflammatory mediators in acute pancreatitis. J Pathol 190:117-125, 2000.)

syndrome (MODS) is determined by the balance of proinflammatory and antiinflammatory cytokines (Figure 12-6).[60]

CLINICAL SIGNS

History

Siamese cats initially were reported to be at increased risk for the disease in one of the first retrospective studies of feline ANP.[2] Clinical case surveys of the past 10 years suggest that most cases of feline pancreatitis are seen in the domestic shorthair breed.[1-10] Anorexia (87 per cent) and lethargy (81 per cent) are the clinical signs reported most frequently in cats with ANP, but these clinical signs are not pathognomonic for ANP (Table 12-2). Anorexia and lethargy are the most important clinical signs in many feline diseases. Gastroenterological signs are sporadic and reported less frequently in affected cats. Vomiting and diarrhea are reported in only 46 per cent and 12 per cent of cases, respectively.[2-7,9,10] In dogs, vomiting (90 per cent) and diarrhea (33 per cent) are more important clinical signs.[12,27,49]

Table 12-2 | **Historical Findings in Cats Affected with Acute Necrotizing Pancreatitis**

FINDING	# OF CASES	INCIDENCE
Anorexia	131/150	87%
Lethargy	129/159	81%
Weight loss	75/159	47%
Vomiting	73/159	46%
Diarrhea	19/159	12%

Data summarized from references 2-7, 9, 10.

Table 12-3 | **Physical Examination Findings in Cats Affected with Acute Necrotizing Pancreatitis**

FINDING	# OF CASES	INCIDENCE
Dehydration	50/92	54%
Hypothermia	23/54	46%
Icterus	51/138	37%
Fever	15/62	25%
Abdominal pain	30/159	19%
Abdominal mass	18/159	11%

Data summarized from references 2-7, 9, 10.

Physical Examination Findings

Physical examination findings in cats with ANP (Table 12-3) include dehydration (54 per cent), hypothermia (46 per cent), icterus (37 per cent), fever (25 per cent), abdominal pain (19 per cent), and abdominal mass (11 per cent).[2-7,9,10] These findings suggest that a "classic textbook" description of ANP (e.g., vomiting, diarrhea, abdominal pain, and fever) is not seen consistently in domestic cats. Many of these physical examination findings are reported more commonly in canine ANP. Abdominal pain (58 per cent in dogs; 19 per cent in cats) and fever (32 per cent in dogs; 25 per cent in cats), for example, are reported more commonly in dogs with ANP.[12,27,49]

DIFFERENTIAL DIAGNOSIS

The major differential diagnoses for feline ANP include gastrointestinal foreign body, inflammatory bowel disease, infectious gastroenteritis, gastrointestinal intussusception and neoplasia, cholangitis, biliary tract neoplasia, and various forms of liver pathology.

DIAGNOSIS

As in dogs, diagnosis of ANP requires the careful integration of historical, physical examination, clinicopathological, and imaging findings. Where appropriate, additional diagnostic support may be obtained at the time of laparoscopy or exploratory laparotomy. Diagnosis should not be made on the basis of a single laboratory or imaging finding.

Laboratory Findings

In cats affected with ANP, laboratory abnormalities (Tables 12-4 and 12-5) have included normocytic, normochromic, regenerative, or nonregenerative anemia (38 per cent);

Table 12-4 | **Hematological Findings in Cats Affected with Acute Necrotizing Pancreatitis**

FINDING	# OF CASES	INCIDENCE
Anemia	39/103	38%
Hemoconcentration	14/82	17%
Leukocytosis	46/99	46%
Leukopenia	14/94	15%

Data summarized from references 2-7, 9, 10.

Table 12-5 | **Serum Biochemical Findings in Cats Affected with Acute Necrotizing Pancreatitis**

FINDING	# OF CASES	INCIDENCE
↑↑ ALT, AST	37/65	57%
↑↑ ALP	32/65	49%
↑↑ Bilirubin	38/65	58%
↑↑ Glucose	32/71	45%
↑↑ Cholesterol	28/39	72%
↓↓ Calcium	55/85	65%
↓↓ Albumin	14/39	36%

Data summarized from references 2-7, 9, 10.

leukocytosis (46 per cent); leukopenia (15 per cent); hyperbilirubinemia (58 per cent); hypercholesterolemia (72 per cent); hyperglycemia (45 per cent); hypocalcemia (65 per cent); hypoalbuminemia (36 per cent); and elevations in serum alanine aminotransferase (57 per cent) and alkaline phosphatase (49 per cent) activities.[2-7,9,10] Changes in red blood cell counts, serum activities of liver enzymes, and serum concentrations of bilirubin, glucose, and cholesterol are fairly consistent findings in ANP in cats, just as they are in dogs.[12,27,49] Important differences between cats and dogs are reflected in white blood cell counts and serum calcium concentrations. Leukocytosis is a more important clinical finding in dogs (62 per cent) than cats (46 per cent).[12,27,49] Leukopenia sometimes is seen instead of leukocytosis in cats, and a worse prognosis has been attributed to leukopenia in cats.[2,5,7,10] Hypocalcemia is a more frequent finding in cats (3 to 5 per cent in dogs[12,49]; 45 to 65 per cent in cats[2,5,6,10]). Hypocalcemia (total and serum ionized) may result from several mechanisms, including acid-base disturbances, peripancreatic fat saponification, and parathormone resistance.[61] Regardless of the mechanism, hypocalcemia confers a worse clinical prognosis in cats.[6,10] This finding suggests that cats should be monitored fairly closely for the development of hypocalcemia, and treatment should be initiated accordingly.

Special Tests of Pancreatic Function

Lipase and Amylase Activity Assays

Serum lipase activities are elevated in experimental feline pancreatitis,[62,63] but serum lipase and amylase activities do not appear to be elevated or of clinical value in the diagnosis of clinical pancreatitis.[64] Serum lipase activity may still have some clinical utility in the diagnosis of ANP in dogs.[65] Assays of serum lipase activity are complicated by the fact that as many as five different isoenzymes may be circulating in the blood[66]; consequently, general serum lipase activity assays have been superseded by the development of pancreatic lipase immunoreactivity assays (e.g., *c*PLI, *f*PLI).[66,67]

Trypsin-like Immunoreactivity (TLI)

Serum TLI measures trypsinogen primarily, but it also detects trypsin and some trypsin molecules bound to proteinase inhibitors.[67] TLI assays are species-specific, and different assays for feline (*f*TLI) and canine (*c*TLI) have been developed and validated.[68] Serum TLI concentration is the diagnostic test of choice for feline exocrine pancreatic insufficiency, because it is highly sensitive and specific for this disease in cats.[11] The use of this test in the diagnosis of feline ANP is less clear. Serum TLI concentrations are elevated transiently in experimental feline acute pancreatitis,[69] but elevations in clinical cases are seen less consistently.[5,7,64] The poor sensitivity (i.e., 33 per cent) of this test precludes its use as a definitive assay for feline ANP.

Trypsinogen Activation Peptide (TAP)

When trypsinogen is activated to trypsin, a small peptide, TAP, is split from the trypsinogen molecule. Under normal conditions, activation of trypsinogen takes place only in the small intestine, and TAP is undetectable in the blood. During ANP, trypsinogen is activated prematurely in pancreatic acinar cells and TAP is released into the vascular space.[67] Urine TAP assays have shown some promise in experimental models of feline pancreatitis,[70] whereas serum TAP assays have shown some utility in preliminary clinical studies.[71] Larger clinical trials are necessary to determine the true specificity and sensitivity of this assay.

Pancreatic Lipase Immunoreactivity (PLI)

A radioimmunoassay for the measurement of feline pancreatic lipase immunoreactivity (*f*PLI) has been developed and validated in cats.[72] *f*PLI elevations have been cited in one preliminary report of experimental[69] and in one clinical[73] report of feline ANP. Larger clinical studies are required to determine the true sensitivity and specificity of *f*PLI in the diagnosis of feline ANP.

Imaging Findings

Radiography

The radiographic hallmarks of canine acute pancreatitis (e.g., increased density in the right cranial abdominal quadrant, left gastric displacement, right duodenal displacement, and gas-filled duodenum/colon)[12,74] have not been substantiated in cats. These radiographic findings were not reported in cats with documented ANP.[1-10] In spontaneous clinical cases, hepatomegaly and abdominal effusion are the only radiographic findings associated with feline ANP.[1-10]

Ultrasonography

Enlarged, irregular, and/or hypoechoic pancreas; hyperechogenicity of the peripancreatic mesentery; and peritoneal effusion have been observed with abdominal ultrasonography in many cats with spontaneous ANP (Figure 12-7).[3-8,10] The specificity of this imaging modality appears to be high (>85 per cent), but the sensitivity has been reported as low as 35 per cent in some studies.[5,7,8] The low sensitivity suggests that imaging the pancreas in cats with ANP is more difficult technically than

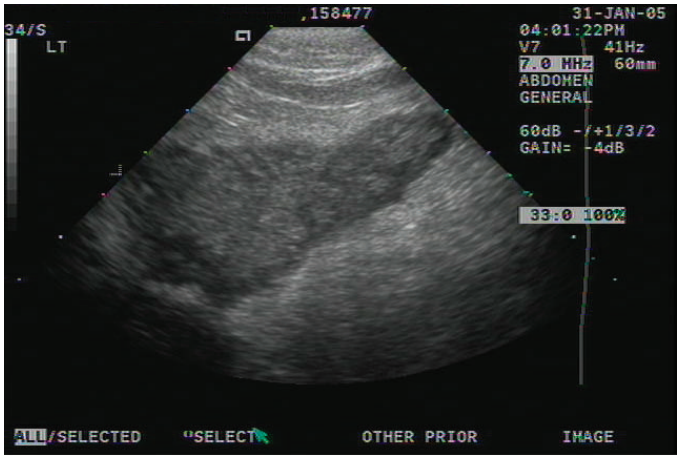

Figure 12-7. Abdominal ultrasound from a 12-year-old neutered male domestic shorthair cat presented with a 3-day history of anorexia, severe depression, and postural changes after a single bout of vomiting. At presentation, the patient was hypothermic and hypotensive, and showed evidence of pain on palpation of the mid-cranial abdomen. On ultrasonography, the pancreas was severely enlarged and hypoechoic, and surrounded by hyperechoic fat. A moderate amount of anechoic effusion was noted within the abdomen, which was determined by cytological examination to be a mild suppurative exudate. (Photograph courtesy Anne Bahr, Texas A&M University.)

imaging the pancreas in dogs, or that the ultrasonographic appearance of ANP in cats differs from that reported for dogs. New diagnostic criteria may be needed if abdominal ultrasonography is to be a more effective tool in the diagnosis of ANP in cats.[8,75]

Computed Tomography (CT)

CT scanning appears to be useful in identification of the normal structures of the healthy feline pancreas,[76] but preliminary clinical reports of feline ANP have been somewhat disappointing.[7,73] The sensitivity of CT scanning in detection of lesions consistent with feline ANP may be as low as 20 per cent.[7,73] Additional study is needed to determine the specificity and sensitivity of this imaging modality in the diagnosis of feline ANP.

Biopsy

If indicated clinically, pancreatic biopsy may be obtained by laparoscopy or exploratory laparotomy. Clinicians should always bear in mind that many patients with pancreatitis are poor anesthetic risks. Gross observation at the time of laparoscopy or exploratory laparotomy may confirm the diagnosis of ANP. In equivocal cases, biopsy may be performed safely as long as blood flow is preserved at the site of the biopsy. Single biopsy may be insufficient to exclude subclinical pancreatitis, because inflammation of the canine pancreas has been shown to occur in discrete areas within the pancreas rather than diffusely throughout the whole organ.[77] Similar findings have been reported in feline ANP.[2] Inspection of other viscera (e.g., intestine, biliary tract, liver) at the time of laparoscopy or exploratory laparotomy is paramount in cats because of the high rate of disease concurrence in this species.*

*References 2,3,9,10,14,20,21.

Table 12-6 | **Clinical Difference Between Feline and Canine Acute Necrotizing Pancreatitis**

	FELINE	CANINE
Vomiting	46%	90%
Diarrhea	12%	33%
Fever	25%	32%
Abdominal pain	19%	58%
↑ WBC's	46%	62%
↓ Ca^{2+}	65%	5%
Radiography	Not useful	Somewhat useful
I.B.D.	Strong association	Weak association

Data summarized from references 2-7, 9, 10, 12.

Table 12-7 | **Treatment of Feline Acute Necrotizing Pancreatitis**

1. Eliminate inciting agent
2. N.P.O.—short duration, and only if severe vomiting
3. Intravenous fluids
4. Supportive therapy—plasma, 10 ml/kg
5. Relieve pain—meperidine, butorphanol
6. Antiemetics—α_2 or 5-HT_3 antagonists
7. Calcium gluconate supplementation
8. H_1 and H_2 histamine receptor antagonists
9. Low-dose dopamine infusion—5 µg/kg/min
10. Broad-spectrum antibiotics
11. Ductal decompression

SPECIES DIFFERENCES

Many important species differences exist between dogs and cats with regard to the clinical course and pathophysiology of ANP (Table 12-6).[27] Fever, leukocytosis, vomiting, and abdominal pain are important physical examination findings in dogs with ANP, but these are relatively infrequent findings in cats with ANP. Cats more often have hypothermic reactions, and they may not necessarily manifest the classic gastroenterological signs (e.g., vomiting, diarrhea, abdominal pain) reported in dogs. The imaging findings in cats also are more subtle than what has been reported in dogs; the classic radiographic hallmarks of canine ANP have not been reported in cats. Cats have a greater incidence and severity of hypocalcemia after bouts of ANP. Serum total and/or ionized hypocalcemia is reported in 45 to 65 per cent of affected cats, whereas hypocalcemia is reported in only 5 per cent of affected dogs. The pathogenesis of hypocalcemia in cats with ANP is incompletely understood, but it does carry a significantly worse prognosis for recovery.[6] Prior gastrointestinal tract disease confers slight increased risk for the development of ANP in dogs[12,49]; this is especially true of cats.[2,10,14,20,21]

THERAPY

Supportive care continues to be the mainstay of therapy for feline ANP (Table 12-7). Efforts should be made to identify and eliminate any inciting agents; sustain blood and plasma volume; correct acid/base, electrolyte, and fluid deficits; place the pancreas in physiological rest for short periods of time; and treat any complications that might develop. Important life-

threatening complications of acute pancreatitis in cats include hypocalcemia, disseminated intravascular coagulation, thromboembolism, cardiac arrhythmia, sepsis, acute tubular necrosis, pulmonary edema, and pleural effusion.

Historically, a short period of fasting of food and water has been recommended for cats with ANP. This recommendation should be applied only in cats with severe vomiting and risk for aspiration pneumonia. Cats otherwise should be fed through bouts of ANP. As obligate carnivores, cats develop fat mobilization and hepatic lipidosis during prolonged starvation. Moreover, recent studies suggest stimulation of pancreatic secretion (via feeding) in affected animals may be appropriate and necessary.[53-56] Esophagostomy, gastrostomy, and enterostomy tubes may be placed to facilitate nutrition in anorectic animals (see Chapter 16).

Other therapies that may be of some benefit in the treatment of this disorder include the following:

- Relief of pain: Analgesic agents should be used when abdominal pain is suspected. Most cats do not manifest overt clinical signs of abdominal pain, but clinicians should be suspicious for it. Meperidine at a dose of 1 to 2 mg/kg IM or SC q2-4h or butorphanol at a dose of 0.2 to 0.4 mg/kg SC q6h has been recommended.[78]
- Antiemetic agents: Nausea and vomiting may be severe in affected animals. The α_2-adrenergic antagonists and 5-HT_3 antagonists appear to be the most effective antiemetic agents in cats.[79] Cats may be treated with chlorpromazine (α_2-adrenergic antagonist) at a dose of 0.2 to 0.4 mg/kg SC or IM q8h, or with any of the 5-HT_3 antagonists (ondansetron 0.1 to 1.0 mg/kg, granisetron 0.1 to 0.5 mg/kg, or dolasetron 0.5 to 1.0 mg/kg PO or IV q12-24h). Dopaminergic antagonists, such as metoclopramide, are less effective antiemetic agents in cats.[79]
- Calcium gluconate supplementation: Hypocalcemia is a frequent complication of feline ANP and is associated with a worse prognosis.[6] Calcium gluconate should be given at doses of 50 to 150 mg/kg IV over 12 to 24 hours, and serum total or ionized calcium concentrations should be monitored during therapy.
- H_1 and H_2 histamine receptor antagonists: Histamine and bradykinin-induced increases in microvascular permeability are associated with the development of hemorrhagic necrosis in experimental feline pancreatitis.[80] Treatment with H_1 (mepyramine, 10 mg/kg) and H_2 (cimetidine, 5.0 mg/kg) histamine receptor antagonists protects against the development of hemorrhagic pancreatitis in these models.[80] Efficacy has not been established in clinical pancreatitis, but the use of these drugs in suspected or proven clinical cases would seem to make sense because they are associated with few side effects. Diphenhydramine (2 to 4 mg/kg) or dimenhydrinate (4 to 8 mg/kg) are other examples of clinically used H_1 histamine receptor antagonists. Cimetidine (5 mg/kg), ranitidine (1 to 2 mg/kg), famotidine (0.5 to 1.0 mg/kg), and nizatidine (2.5 to 5.0 mg/kg) are examples of clinically used H_2 histamine receptor antagonists.
- Low-dose dopamine infusion: Low-dose dopamine infusion (5 µg/kg/min) improves pancreatic blood flow and reduces microvascular permeability in feline experimental pancreatitis.[63] Low-dose dopamine infusion is effective treatment in experimental pancreatitis when it is given up to 12 hours after induction of the disease.[63] Part of the appeal of dopamine as a potential treatment for feline APN lies in the diversity of its actions. Dopamine's effect on the kidney in promotion of renal blood flow and urinary output and its cardiac inotropic effect make it an ideal agent, although it has not yet been studied in controlled clinical trials.
- Broad-spectrum antibiotics: ANP may begin as a sterile process, but necrosis and inflammation predispose to colonic bacterial translocation and colonization of the pancreas.[81,82] *E. coli* and other coliforms are the principal pathogens.[81,82] High colonization rates suggest that bacteria may spread to the inflamed pancreas more frequently than is currently thought and that broad-spectrum antibiotics may be appropriate in suspected cases of feline acute pancreatitis. Cefotaxime at a dose of 50 mg/kg IM q8h prevents bacterial colonization of the pancreas.[83]
- Ductal decompression: Surgical decompression of the pancreaticobiliary duct should be considered in cases of acute ductal obstruction, such as calculus, neoplasia, and fluke infection. Ductal decompression also may be useful in acute cases that have progressed to the more chronic form of the disease. Ductal decompression has been shown to restore pancreatic blood flow, tissue pH, and acinar cell function.[31,32]

PREVENTION

In cases in which IBD is the underlying pathogenesis of ANP, therapy should be directed eventually toward regulation of the IBD. The five components of feline IBD therapy are dietary modification, antibiotics, probiotics, antidiarrheal agents, and immunosuppressive therapy.[84]

COMPLICATIONS

Chronic Nonsuppurative Pancreatitis

Recurring bouts of ANP may progress to a chronic nonsuppurative form of the disease. This chronic form of pancreatitis generally has been held to be of lesser clinical severity, lower mortality, and better long-term prognosis.[1] More recent reports suggest, however, that chronic pancreatitis cannot be differentiated from acute pancreatitis by clinical, clinicopathological, or imaging findings.[10] The clinical signs, laboratory data, and imaging findings are indistinguishable between the two groups. Histopathology remains the only dependable method of differentiating acute and chronic pancreatitis. Not surprisingly, cats with chronic pancreatitis more frequently have concurrent systemic disease (e.g., cholangitis, IBD) compared with cats with acute pancreatitis.[10]

Exocrine Pancreatic Insufficiency (EPI)

EPI is an uncommon cause of chronic diarrhea in cats. Insufficiency results from failure of synthesis and secretion of pancreatic digestive enzymes. The natural history of feline EPI is

poorly understood, but most cases are believed to result from chronic pancreatitis, fibrosis, and acinar atrophy. As with dogs, clinical signs reported in cats with EPI include weight loss, soft voluminous feces, and ravenous appetite. Affected cats may have an antecedent history of recurring bouts of acute pancreatitis (e.g., anorexia, lethargy, vomiting) culminating in chronic pancreatitis and EPI.

The diagnosis of EPI in cats has been technically difficult. Clinical signs in affected cats are not pathognomonic for EPI, clinicopathological data are fairly nonspecific, imaging findings are inconsistent, and the severity of pancreatic histological changes is not always related directly to the severity of clinical signs. One study suggests that serum TLI may be useful in the diagnosis of this disease.[11] In that study, TLI concentrations less than 8 µg/L (reference range = 17 to 49 µg/L) were reported in 17 out of 20 cats with clinical signs compatible with EPI (e.g., weight loss, loose voluminous feces, greasy soiling of the hair coat) and at least one other finding, such as decreased fecal proteolytic activity, exploratory laparotomy or necropsy findings compatible with EPI, or favorable response to pancreatic enzyme replacement therapy. Cats affected with EPI have predictable serum cobalamin deficiency because of pancreatic intrinsic factor deficiency and cobalamin malabsorption[85] (see Chapter 13). Therapy should include subcutaneous vitamin B_{12} injections (100 µg SC every 3 to 4 weeks) in addition to pancreatic replacement enzymes.

Hepatic Lipidosis

ANP is one of many examples in which anorexia or starvation predisposes an obligate carnivore to the syndrome of fat mobilization and hepatic lipidosis.[1,3,86] The concurrence of these two syndromes is a particularly poor prognostic sign in that affected cats have high morbidity and mortality rates.[3] This emphasizes the importance of early interventions in the treatment of pancreatitis before the development of the metabolic syndrome of hepatic lipidosis.

Diabetes Mellitus

Several studies have related severe chronic pancreatitis to the development of diabetes mellitus.[1,4,10,11] ANP *per se* may not necessarily be a risk factor for the development of diabetes mellitus, but disease progression to the chronic nonsuppurative form may increase that risk.

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Chapter 13

Cobalamin in the Diagnosis and Treatment of Chronic Gastrointestinal Disease

Craig G. Ruaux

Cobalamin is a member of the B-group, water-soluble vitamins. It was known originally as vitamin B_{12}; however, modern vitamin nomenclature prefers the use of the term cobalamin. Cobalamin is unique among biological compounds: it has a stable carbon-cobalt bond in the structure. Cobalamin has a highly complex structure, the most complex structure known for any vitamin at this time.

The importance of cobalamin, although the compound itself was unknown at the time, was suggested initially by investigations into the pathology and treatment of pernicious anemia in the early part of the twentieth century. In the early to mid-1920s, George H. Whipple showed that dogs with anemia (induced by bleeding the dogs) recovered from their anemia more rapidly when fed a liver-based diet.[1,2] Building on Whipple's work, Minot and Murphy, two Boston physicians, found that the consumption of large quantities of slightly cooked liver could cure human patients with pernicious anemia. As pernicious anemia previously was considered invariably fatal, the discovery of the liver diet marked a significant step forward in the treatment of this disease.[1,2] An enormous effort was started to identify the "liver factor," which led eventually to the purification and crystallization of pure cobalamin in 1948.[2]

Recent evidence indicates that subnormal cobalamin availability in cats with gastrointestinal disease may play a significant role in reduction of the effectiveness of medical therapy for these cats. The aim of this chapter is to describe the use of cobalamin as a diagnostic marker for small intestinal disease in cats and the importance of cobalamin supplementation in cats with gastrointestinal disease and low serum cobalamin concentrations.

BIOLOGICAL ROLES OF COBALAMIN

Although cobalamin was identified originally as a result of studies of human beings with anemia, the main biological role of cobalamin is as a cofactor in bacterial metabolism. Only three known enzyme systems exist in mammals with an obligate requirement for cobalamin as a cofactor, whereas many more enzyme systems in bacteria require this compound.[3]

Most cobalamin-dependent reactions involve the transfer of relatively simple functional groups, such as a methyl ($-CH_3$) group. Figure 13-1 illustrates the cobalamin- and folate-dependent action of methionine synthase, one of the cobalamin-dependent enzymes found in bacterial and mammalian cells.

In addition to the transfer of functional groups from one compound to another, such as the transfer of a methyl group from 5′-tetrahydrofolate to homocysteine, an additional class of cobalamin-dependent enzymes catalyzes the structural rearrangement of simple compounds. These isomerases and mutases are important in bacterial fermentation reactions. At least one, methylmalonyl-CoA-mutase, is important in bacteria and eukaryotes for the terminal degradation of some amino acids and branched-chain fatty acids, which allows their entry into the Krebs cycle and thus generates ATP (Figure 13-2).[4]

Cobalamin-dependent reactions occur typically in the mitochondria, and the serum concentration of cobalamin is not necessarily an accurate indicator of the cobalamin status of the patient. Methlymalonic acid is considered to be an accurate measure of cobalamin availability at the cellular level.[4]

SOURCES OF COBALAMIN

All cobalamin in the environment arises from bacterial synthesis. Many bacterial species present in the large intestine of most animal species, including carnivores, are able to synthesize cobalamin. Ironically, the exclusive site of cobalamin absorption is cranial to the large intestine, and the bacterially synthesized cobalamin present in carnivore feces is unavailable to the host organism.

Herbivorous animals, such as ruminants, host cobalamin-synthesizing bacteria in the rumen or equivalent foliage-

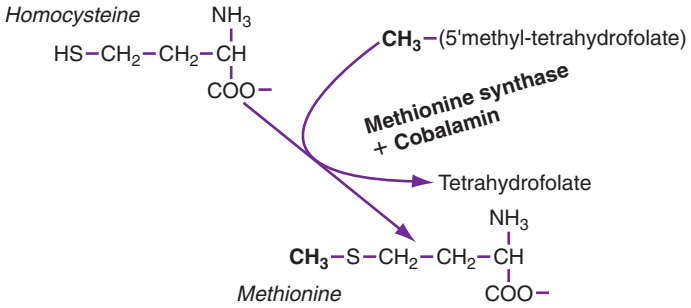

Figure 13-1. Illustration of the action of methionine synthase, a cobalamin-dependent enzyme. The transferred single carbon group is shown in boldface. This methyl group is obtained from 5′-tetramethylhydrofolate; therefore, normal activity of the methionine synthase enzyme requires both adequate cobalamin and folate intake.

fermenting organ. Cobalamin synthesized by the herbivore's intestinal bacteria is absorbed and accumulates in the body, bound to muscle and organ tissue proteins. Obligate carnivores, such as cats, obtain their cobalamin requirements from the consumption of organ tissues and muscle protein. Herbivore livers are a particularly rich source of cobalamin. Typical commercially produced cat diets are rich in cobalamin because they are based on offal/organ tissue and muscle proteins with the addition of vitamin premixes. Dietary deficiency leading to cobalamin deficiency thus is highly unlikely in cats. Experimental induction of cobalamin deficiency in cats requires the use of a highly specialized, rigidly specified diet.[5]

This combination of diets rich in cobalamin and the highly specialized mechanisms of cobalamin absorption described below allows the use of cobalamin as a diagnostic marker for small intestinal disease.

ABSORPTION AND TRANSPORT

Normal cobalamin absorption relies on normal gastric, pancreatic, and ileal function. In companion animals, disturbances in pancreatic or ileal function are the most common causes of decreased cobalamin absorption. The absorption mechanism for dietary cobalamin is illustrated in Figure 13-3.

Dietary cobalamin, bound initially to protein in the diet, is liberated in the stomach by the action of pepsinogens and gastric acid. Immediately after the cobalamin is released, it binds to gastric and salivary "R-proteins," which carry the cobalamin into the duodenum. In the duodenum, the R-protein–cobalamin complex is broken down by pancreatic proteases, and the newly liberated cobalamin is taken up by another carrier protein, "intrinsic factor." The site of intrinsic factor synthesis and secretion varies from species to species. In human beings, the gastric mucosa is the major source of intrinsic factor, whereas dogs produce intrinsic factor in both the stomach and the pancreas.[6] Domestic cats synthesize intrinsic factor exclusively in the exocrine pancreas.[7,8]

Because the exocrine pancreas is the only source of intrinsic factor in cats, exocrine pancreatic insufficiency commonly is associated with cobalamin deficiency in that species and should be ruled in or out using the serum feline trypsin-like immunoreactivity assay (*f*TLI) in patients with gastrointestinal signs and a decreased serum cobalamin concentration.[9]

Highly specialized cobalamin–intrinsic factor complex receptors are expressed on ileal mucosal enterocytes. Cobalamin not bound to intrinsic factor is not readily absorbed, even if given orally in high doses.

Cobalamin Half-Lives in Health and Disease

Once absorbed, cobalamin undergoes enterohepatic circulation. Disease of the distal small intestine decreases the ability of cats to reabsorb the cobalamin that is secreted in the bile; therefore the half-life of circulating cobalamin is decreased in cats with gastrointestinal disease. Studies that use radiolabeled cyanocobalamin given by parenteral injection showed that the half-life of cobalamin in healthy cats is approximately 13 days, whereas in two cats with inflammatory bowel disease, the half-life was reduced to approximately 5 days.[10]

The presence of enterohepatic cycling of cobalamin leads to a need for ongoing cobalamin supplementation in cats with gastrointestinal disease, even after symptomatic relief with medical and dietary therapy.

Use of Cobalamin as a Diagnostic Marker

Cobalamin is absorbed via a highly complex sequence of carrier proteins and a specialized receptor mechanism that is restricted to the ileum.[7,10] As a result of this strict anatomical localization of cobalamin absorption, and the presence of an enterohepatic circulation of cobalamin, the serum cobalamin concentration reflects the rate of absorption of cobalamin from the distal small intestine. Serum cobalamin concentrations can be used as a marker of distal or diffuse small intestinal disease.

Although cobalamin deficiency is a sensitive indicator of reduced small intestinal cobalamin uptake, the presence of a subnormal serum cobalamin concentration is not specific for any one small intestinal disorder. Abnormalities in production of any of the various carrier proteins or receptors, loss of recep-

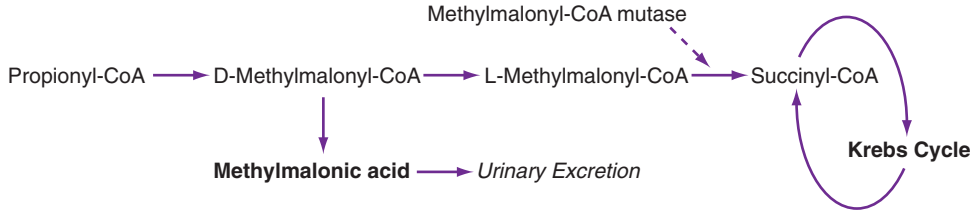

Figure 13-2. The importance of methylmalonyl-CoA-mutase in the terminal degradation reactions of amino acids and some fatty acids via propionyl-CoA to enter the Kreb's cycle. Deficiency of cobalamin leads to accumulation of D-methylmalonyl-CoA, which is converted to methylmalonic acid and excreted in the urine. This reaction is dependent on cobalamin but not folate.

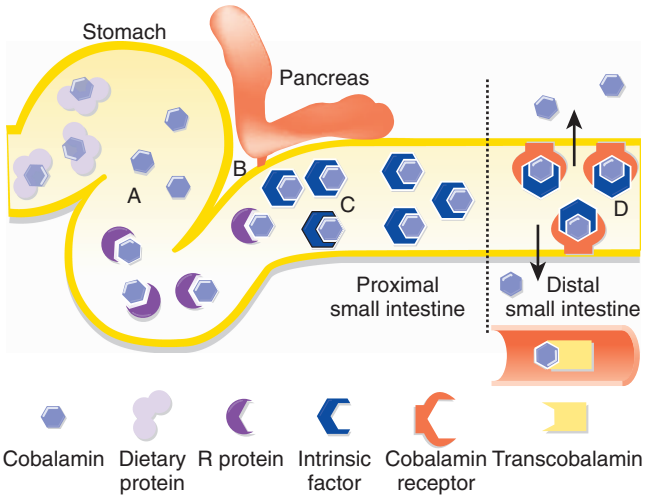

Figure 13-3. The absorptive mechanism for dietary cobalamin. Cobalamin enters the gastrointestinal tract bound to dietary protein. In the stomach, pepsin and hydrochloric acid degrade the dietary protein, releasing the cobalamin **(A).** The cobalamin is bound immediately by R-protein, which is produced in the stomach mucosa and is transported in this form to the duodenum. In the duodenum, pancreatic proteinases digest the R-protein and release the cobalamin. Free cobalamin in the duodenum is bound yet again by intrinsic factor for transport to the distal small intestine **(B).** In dogs and human beings, both the stomach and the pancreas produce intrinsic factor; in cats, only the pancreas produces intrinsic factor. Cobalamin remains bound to intrinsic factor during passage through the proximal small intestine **(C).** In the distal small intestine, the cobalamin/intrinsic factor complexes are taken up by specific receptors found only on enterocytes in the ileum **(D).** The enterocytes process the intrinsic factor/cobalamin complex and release cobalamin into circulation, where a final set of binding proteins (transcobalamins) complex the vitamin and carry it to the cells. (Reproduced with permission from *Clinical Techniques in Small Animal Practice* 1(4):203-210, 2003.)

tors on the ileal mucosa, and competition within the gastrointestinal tract between the endogenous microflora and the host can lead to reduced cobalamin availability to the host animal.

MEASUREMENT OF SERUM COBALAMIN CONCENTRATIONS

The measurement of serum cobalamin concentrations is relatively complicated and not feasible in a clinical environment. Traditionally, the method of choice for the measurement of cobalamin is via bacterial bioassay. Numerous bacterial species require cobalamin for growth. In a bacterial bioassay, cobalamin is measured by serial dilution of the sample in growth medium. The greatest dilution capable of supporting the growth of the bacterium is determined, and the cobalamin concentration in the original sample is back-calculated from the dilution. Obviously, this is a time-consuming and expensive assay and is available only from a limited number of specialist laboratories.

More automated immunoassay methods have been developed for the determination of cobalamin in serum, and these assay methods are becoming more widely available. These methods rely typically on competition between cobalamin in the sample and a labeled cobalamin analogue. The cobalamin in the sample and the cobalamin analogue compete for intrinsic factor that is immobilized in some manner. Radioimmunoassay and chemiluminescence immunoassay techniques have been described, and both are capable of valid measurement of cobalamin in feline serum. A heat denaturation step is necessary to reduce competition for the cobalamin from other cobalamin-binding proteins in the serum. This step may not be necessary in some assay systems when human serum cobalamin concentrations are being measured, but is important in measurement of feline serum cobalamin concentrations. The laboratory measuring feline serum cobalamin concentrations must have previous experience with these methods. Reference ranges should be established for each laboratory's specific methodology, rather than relying on published reference values, because differing methods of measuring serum cobalamin concentrations may give divergent values.

PREVALENCE OF COBALAMIN DEFICIENCY IN CATS WITH GI DISEASE

The exocrine pancreas is the only known source of intrinsic factor in cats.[7] Because intrinsic factor is essential to the absorption of cobalamin, exocrine pancreatic insufficiency in cats is associated with a high risk for cobalamin deficiency.[9]*

Only a single case report exists in the literature of congenital cobalamin malabsorption in a cat.[11] This contrasts with the situation in dogs, in which well-recognized familial disorders in cobalamin absorption or transport have been described in multiple breeds.[12-16]

By far the most common cause of cobalamin deficiency in domestic cats is the presence of small intestinal mucosal disease, such as inflammatory bowel disease. The prevalence of cobalamin deficiency in these cats, when defined as the presence of elevated serum concentrations of methylmalonic acid (discussed below), approaches 70 per cent in cats with reduced circulating concentrations of cobalamin in the serum. Overall, reduced serum cobalamin concentrations are detected in approximately 28 per cent of cat serum samples submitted for cobalamin determination as part of the workup for gastrointestinal disease. Taken together, these data indicate that cobalamin malabsorption secondary to gastrointestinal disease is a common, but frequently unrecognized, component of chronic gastrointestinal disease in cats. The actual biochemical and clinical consequences of this cobalamin deficiency, when present in cats with gastrointestinal disease, have been defined only recently.

CLINICAL CONSEQUENCES OF COBALAMIN DEFICIENCY

The clinical effects of cobalamin deficiency vary between species. In human beings, cobalamin deficiency leads to anemia, hyperhomocysteinemia, demyelination disorders, and dementia.[17-19] In cats, clinical signs of cobalamin deficiency are not well defined. Unlike in human beings, in whom signs of cobalamin deficiency can develop over extended periods (years in the case of vegans with peripheral demyelination) as a result

*Exocrine pancreatic insufficiency, although recognized with increasing frequency with the recent availability of a specific feline TLI test, is still a relatively uncommon diagnosis in cats with chronic gastrointestinal disease. Exocrine pancreatic insufficiency is diagnosed in cats at approximately one tenth the frequency in dogs (estimated, based on accessions to the service laboratory of the Gastrointestinal Laboratory at Texas A&M University).

of inadequate dietary intake, cobalamin deficiency in cats occurs almost invariably as a result of significant primary gastrointestinal disease. The clinical signs of this gastrointestinal disease, whether exocrine pancreatic insufficiency, inflammatory bowel disease, or an infiltrative neoplastic condition, tend to dominate. The occurrence of cobalamin deficiency in cats with gastrointestinal disease is well documented,[8,10] but efforts to characterize the clinical effects of this deficiency in isolation from the primary disease have been described only recently.[20]

All cells in the body require cobalamin, including the enterocytes, and cobalamin deficiency is associated with changes in gastrointestinal mucosal permeability, absorptive function, and histopathological appearance in human patients with pernicious anemia.[21] Gastrointestinal mucosal structure and function normalize in these patients after institution of parenteral cobalamin therapy.[21] Similar studies have not been reported in companion animals; however, empirical experience suggests that animals that present with gastrointestinal disease and low serum cobalamin concentrations are often less responsive to therapy for their disease if they are not treated concurrently with cobalamin. This refractory nature of chronic gastrointestinal disease also, empirically, appears to resolve in some cases with parenteral cobalamin supplementation.

Deficiency of cobalamin, at the cellular level, leads to a reduction in the activity of cobalamin-dependent enzyme systems. In human beings, cobalamin deficiency may be associated with a resting hyperhomocysteinemia, which results from reduced activity of the methionine synthase enzyme. In cats, hyperhomocysteinemia is not seen typically in sera from fasted cats, even when serum cobalamin concentrations are extremely low or undetectable.[8]

Reduced activity of methylmalonyl-CoA mutase leads to an accumulation of methylmalonyl-CoA. This feeds back subsequently on a branch point in the terminal degradation of several amino acids, which leads to the increased production of methylmalonic acid. This methylmalonic acid subsequently is excreted in the urine (see Figure 13-2). Cats with severely subnormal serum cobalamin concentrations typically show extreme elevations in serum methylmalonic acid concentrations. In some cases a 50-fold elevation over the highest normal value may be documented.[8]

In a short-term study investigating the effects of cobalamin supplementation on cats with severe hypocobalaminemia, marked changes in serum concentrations of methylmalonic acid were seen.[20] After 4 weeks of parenteral cobalamin therapy using the doses described below, the median serum concentration of methylmalonic acid decreased thirteenfold. Most cats in this study showed a decline in methylmalonic acid to within the reference range for healthy cats after 4 weeks of cobalamin supplementation.

Overall, the supplemented group of cats showed a significant increase in body weight over the 4 weeks of parenteral cobalamin therapy. Not all cats gained weight; however, some maintained the same body weight over the 4 weeks, and some showed significant declines in body weight. Overall, twice as many cats gained weight over the 4 weeks of cobalamin therapy than lost weight.[20]

Along with the improvement in biochemical parameters, owner-reported signs of gastrointestinal disease, such as vomiting and diarrhea, improved in approximately 50 per cent of the cats after supplementation with cobalamin. Because no untreated controls were in the study, the possibility exists that other factors, such as recent diet changes or recent changes in medical therapy, may have been responsible for a proportion of the owner-perceived improvements in clinical status of the cats.[20]

An important issue to be considered in the interpretation of the results of this study is that the therapies the cats were receiving before entry into the study varied markedly. Also their prestudy therapy was maintained without change during the course of the trial. For some cats, this meant that antiinflammatory therapy was administered at higher doses and for longer periods than would typically be the case, whereas other cats received no specific therapy for their gastrointestinal disease and received only the cobalamin supplementation.

Because none of the cats in the study had exocrine pancreatic insufficiency, the source of their cobalamin deficiency is most likely through loss of ileal cobalamin absorption secondary to significant gastrointestinal disease. Unlike human beings with pernicious anemia and secondary small intestinal disease, simple supplementation of a cobalamin-deficient cat without effective diagnosis and treatment of the gastrointestinal disease that has led to the low cobalamin absorption should not be expected to be curative. In this scenario, the cobalamin deficiency and subsequent biochemical and clinical consequences of this cobalamin deficiency are a secondary effect of the cat's gastrointestinal disease.

Cobalamin Supplementation in Deficient Cats

Cobalamin is available as a single-agent injectable or in solutions fortified additionally with other B-group vitamins. Assessing the amount of cobalamin actually present is important, because many B-complex formulations contain relatively low amounts of cobalamin and necessitate excess injection volumes to deliver the necessary amount of cobalamin. B-complex preparations also are more likely to sting on injection, whereas pure cobalamin alone usually does not cause pain or irritation on injection. Because of the variation in cobalamin concentrations and potential for irritation, single-agent preparations of cobalamin are recommended.

Cobalamin preparations are relatively inexpensive and readily available. The typical preparation contains 1000 µg/ml, or 1 mg/ml, cobalamin in solution. Some higher concentration preparations have been marketed, up to 5000 µg/ml. The higher concentration preparations necessitate a smaller injection volume, which may complicate the use of these preparations.

The currently recommended dose of cobalamin is 250 µg/cat by subcutaneous injection, in cats up to 5 kg bodyweight. A course of injections is given at gradually declining frequency, as described in Table 13-1. Very large cat breeds, such as the Maine coon, may need 500 µg/injection if the cat is significantly heavier than 5 kg bodyweight.

All forms of cobalamin are detected by all of the currently available methods for the determination of serum cobalamin; therefore assessing the ability of the cat to absorb dietary cobalamin during the first 12 weeks of treatment is difficult. In a healthy cat with normal cobalamin absorption from the ileum and normal enterohepatic circulation, it takes approximately 78 days (6 half-lives of 13 days) for serum cobalamin to return to a "baseline" concentration after injection of cobalamin.

In cats with gastrointestinal disease, as discussed previously, the half-life of cobalamin is shortened dramatically. Assuming

Table 13-1 | **Recommended Dosage Scheme for Domestic Cats* with Cobalamin Deficiency**

TIME PERIOD	DOSE FREQUENCY	DOSE
Diagnosis to 6 weeks post diagnosis	One dose per week	250 µg
6 weeks post diagnosis to 12 weeks post diagnosis	One dose every second week	250 µg
12 weeks post diagnosis onwards	One dose every 4 to 6 weeks	250 µg

*Cats up to 5 kg body weight.

a half-life of 3 days, as reported previously,[10] the serum concentration of cobalamin will return to the pretreatment baseline in approximately 18 days. Thus assessment of the small intestinal absorptive capacity for cobalamin is feasible once the cat is receiving cobalamin injections every 4 weeks, if a sample is drawn before the cobalamin is administered.

Cats with severe gastrointestinal disease are highly likely to become depleted of cobalamin within a 4-week period after cobalamin injection. Cats with less severe gastrointestinal disease are still likely to become cobalamin depleted over time; therefore regular monitoring of serum cobalamin concentrations is prudent in cats with chronic gastrointestinal disease.

Cobalamin and folate interact intimately at the cellular level, as shown in Figure 13-1. Deficiency of cobalamin may reduce the amount of folate used. In the previously described study of cobalamin supplementation in cats with severe hypocobalaminemia, a significant decline in serum folate concentrations was noted after 4 weeks of cobalamin therapy. In some cases the serum folate declined from low normal to significantly decreased. The clinical consequences of folate deficiency are not well defined in adult cats, and the potential clinical impact of this decline in folate availability currently is unknown.

Because receptors for folate are found only on enterocytes in the proximal small intestine, subnormal serum folate concentrations are considered generally indicative of proximal small intestinal disease.[22] The serum concentration of folate represents a balance between the rate of folate absorption in the proximal small intestine and the rate of consumption of folate in the body's biochemical processes. If bodywide folate consumption is reduced, as appears to occur with cobalamin deficiency, the serum folate concentration may be normal in the face of decreased absorption from the intestine. This may result in a clinically misleading interpretation of the serum vitamin concentrations, which suggests the disease is localized to the distal small intestine, when in fact the disease process is present diffusely throughout the small intestine.

When a patient is cobalamin deficient, all cells in the body are in a state of cobalamin deficiency and may be limited in their growth and division. Neoplastic cells also require cobalamin, and cobalamin deficiency theoretically may reduce the rate of growth and aggressiveness of lymphoid neoplasms.[23,24] Although uncommon, case reports in the human literature have described rapid progression of neoplastic disease in patients with cobalamin deficiency after the institution of cobalamin therapy.[25] This emphasizes the importance of thorough medical investigation, including endoscopic or surgical biopsies, for cats with gastrointestinal disease and cobalamin deficiency. The clinician must remain alert to the possibility that previously undiagnosed neoplastic disease is present in the patient and monitor the clinical progress of the cat closely during the initial stages of cobalamin therapy.

Current Recommendations

Although the results of our recent short-term study of cobalamin supplementation demonstrate that cobalamin deficiency is a contributor to the poor health of some cats with gastrointestinal disease, cobalamin supplementation alone is not expected to be an effective medical therapy for gastrointestinal disease in cats with hypocobalaminemia.[20] Thorough medical investigation of affected cats and the institution of effective medical or dietary therapies for the primary disease are necessary for adequate patient response. Unless the gastrointestinal disease in the patient is resolved completely by medical therapy, the cat will continue to have reduced cobalamin uptake from the small intestine. Therefore long-term supplementation usually is necessary.

Although our prospective study deliberately examined cats with severe hypocobalaminemia (essentially undetectably low serum cobalamin at presentation), not all cats with gastrointestinal disease present with such low serum concentrations of cobalamin. Related work in our laboratory has shown the frequent occurrence of cobalamin deficiency in cats with less marked reductions in serum cobalamin, and in many cats with serum cobalamin concentrations at the lower end of our reference range.[26] Therefore we currently recommend cobalamin supplementation for all cats with gastrointestinal disease and a serum cobalamin concentration less than 300 ng/L. After cobalamin supplementation, patients should be evaluated for potential changes in folate status.

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Chapter 14

Clinical Staging for Inflammatory Bowel Disease

Albert E. Jergens and John M. Crandell

Feline inflammatory bowel disease (FIBD) is an important disorder characterized by persistent gastrointestinal signs, histological evidence of mucosal inflammation, and general responsiveness to immunotherapeutic intervention.[1-3] Clinical signs are variable; disease severity results from numerous factors: the presence or absence of active mucosal inflammation, organ(s) of involvement, physiological (e.g., anemia or vitamin deficiencies) consequences (see Chapter 13), and empirical therapies.[3,4] At present, assessment of FIBD activity depends on a compendium of clinical, radiographic, endoscopic, and histological criteria that vary among clinicians.[1-4] The development of a standardized scoring index, such as those used in human inflammatory bowel disease, would be useful in the management of clinical patients, both as a measure of initial disease burden and an assessment of treatment responses.[5]

This chapter provides a synopsis of current strategies used to assess FIBD activity. It contains a summary of previous clinical findings, report of observations obtained from a recent retrospective study of FIBD, and proposal for a simple numerical index for measurement of clinical disease activity in FIBD.

CURRENT CLINICAL PERSPECTIVE

Etiopathogenesis

Although the etiology is unclear, new information suggests that IBD in human beings results from complex interactions between host susceptibility, mucosal immunity, and the enteric microflora. In susceptible animals, IBD may arise because of a breakdown in the regulatory constraints on mucosal immune responses (loss of tolerance) to enteric bacteria. Both clinical observations and animal models implicate the resident bacterial flora as an essential cofactor in driving the inflammatory response of IBD. Clinical improvement and decreased intestinal inflammation are observed in human beings with IBD when intestinal bacterial concentrations are decreased by antibiotic administration.[6,7] Strong serological antibody activity to several bacterial species is observed in patients with IBD.[8] Furthermore, experimental colitis generally fails to develop when mice in these laboratory models are maintained in germ-free conditions.[9]

Because intestinal inflammation occurs against this "background" of crosstalk between the resident bacterial flora and the mucosal immune response, therapeutic strategies aimed at altering the flora may influence mucosal immunophysiology. Modulation of the enteric microenviroment has been shown recently to reduce proinflammatory mucosal cytokines (thereby attenuating intestinal inflammation) in human patients with Crohn's disease.[10]

Relevant Diagnostic Testing

A diagnosis of IBD is one of exclusion and requires elimination of many other diseases that may cause intestinal inflammation (Table 14-1). Systemic diseases, chronic parasitism, dietary sensitivity (e.g., food allergy or intolerance), infectious diseases, and alimentary lymphosarcoma are the major differential diagnoses for IBD. Objective criteria for diagnosis of FIBD have been described. Clinical signs *must* be correlated with histological evidence of gastroenteritis, and other causes for chronic mucosal inflammation must be eliminated by appropriate diagnostic testing. Therapeutic trials using anthelmintics or hypoallergenic diets may be effective in animals that have parasitic or dietary causes, respectively, for enterocolitis. One recent study indicates that up to 30 per cent of cats with idiopathic gastrointestinal problems may have food sensitivities.[11]

Therapeutic Strategies in FIBD

Therapy for FIBD generally includes dietary modification and the use of immunomodulating drugs to reduce mucosal inflammation. Well-designed therapeutic trials have not been performed in cats with IBD, and therapy remains largely empirical, influenced by the rapidity of clinical remission, the severity of adverse drug effects, client/patient compliance, and drug costs.

General agreement exists that elimination diets or novel protein, highly digestible diets are beneficial in cats with IBD. A bigger question is *which* specific dietary components are most important in the pathogenesis or management of this disease. Several dietary constituents of potential relevance in FIBD have been identified (Table 14-2). Additionally, the

Table 14-1 | **Diagnostic Tests for Intestinal Inflammation**

TEST	RULEOUT
Controlled diet	Food allergy/intolerance
Fecal examination	Nematodes, protozoa, fungal
Serum T_4	Feline hyperthyroidism
FeLV/FIV serology	FeLV/FIV infection
Endoscopic biopsy	Neoplasia, fungal, algal
Endoscopic cytology	Neoplasia, fungal, algal?
Celiotomy/biopsy	Neoplasia, fungal, algal

FeLV, Feline leukemia virus; *FIV*, feline immunodeficiency virus.

Table 14-2 | **Dietary Constituents of Potential Relevance in IBD**

CONSTITUENT	RELATIVE MERITS
Protein	Novel, highly digestible proteins are best
Fat	n-3 FA may ↓ intestinal inflammation
Fiber	Soluble fiber makes beneficial SCFA
Glutamine	Promotes epithelial integrity
Gluten	Promotes dietary sensitivity
Lactose	Contributes to osmotic diarrhea
Cobalamin	Supplement as needed
Probiotics	Beneficial microbes may ↓ inflammation

FA, Fatty acids; *SCFA*, short chain fatty acids.

Table 14-3 | **Pharmacotherapy for FIBD**

Prednisone/prednisolone*	1-3 mg/kg PO q12 h
Metronidazole*	10 mg/kg PO q24 h
Azathioprine	0.5 mg/kg PO q12 h
Sulfasalazine	20 mg/kg PO q12 h
Chlorambucil	1-2 mg/m^2 PO q48 h

*First choice drugs.

benefits of dietary fiber, the use of polyunsaturated fatty acids (n-3 fatty acids), and prebiotic/probiotic supplementation to affect endogenous gut flora have not been investigated fully.

Dietary management alone for IBD is seldom successful, and most cats require pharmacological therapy (Table 14-3). Most drug therapies interrupt the amplification sequence of inflammation in IBD, which explains why maintenance therapy (via diet and/or drugs) is important. Anecdotal evidence supports the use of oral corticosteroids, azathioprine or chlorambucil, and metronidazole in therapy of FIBD.

Current Measures of Disease Activity in FIBD

The exclusion of IBD mimics, coupled with histology, constitute the primary tools for diagnosis of FIBD, and a combination of endoscopic and imaging techniques defines disease distribution. Disease activity presently is assessed by numerous factors (Figure 14-1). However, several problems exist with this system. First, clinical severity is subjective, depending heavily on the client's perception of the disease. Second, diagnosis often is based on poorly standardized histological grading criteria. Third, evaluation of immunological parameters (e.g., immune cell populations and inflammatory mediators) is technically cumbersome and impractical for routine clinical use. Our current knowledge base for defining FIBD activity is based on the following.

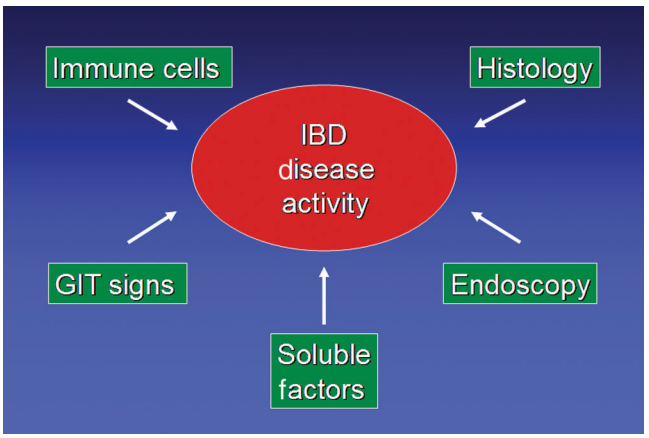

Figure 14-1. Current indices for assessment of disease activity in cats with inflammatory bowel disease. *GIT*, Gastrointestinal tract.

Gastrointestinal Endoscopy

Only limited data exist concerning the prevalence of mucosal abnormalities observed endoscopically in cats with IBD. A survey of the largest case-based studies performed indicates that increased granularity, increased friability, and erosions are the predominant mucosal lesions with FIBD (Figure 14-2).[2,12-14] Taken together, these earlier reports indicate that endoscopic lesions involving gut mucosa are present in approximately 42 per cent of cats with IBD.

Histological Grading

Histological examination of mucosal biopsy specimens is *essential* for diagnosis of FIBD. Unfortunately, uniform and objective morphological criteria for diagnosis of FIBD have not been established. Biopsy interpretation shows considerable interobserver variability between pathologists and is further hampered by the technical constraints of specimen size and procurement/processing artifacts inherent in evaluation of endoscopic specimens.[15,16] Several histological grading schemes have been described for evaluation of endoscopic specimens obtained from cats with IBD.[2,12-14,17] Most studies have relied on semiquantitative[14] or quantitative[17] evaluation of lamina proprial cellularity, whereas other investigators (including the authors) have employed more objective parameters of mucosal inflammation, including increased epithelial lymphocytes, altered mucosal structure, and changes in the surface epithelia (Figure 14-3).[2,12,15,18]

Mucosal Immune Cells

Characterization of feline mucosal immunology has occurred only to a limited extent. In separate studies, increased lamina propria myeloid/histiocyte antigen-positive macrophages[19] and upregulated epithelial MHC class II molecule expression[20] have been observed, suggesting an underlying immune-based etiology for FIBD.

Inflammatory Mediators

Upregulation of mucosal cytokines in FIBD has been correlated recently to morphological changes (e.g., villus atrophy/fusion,

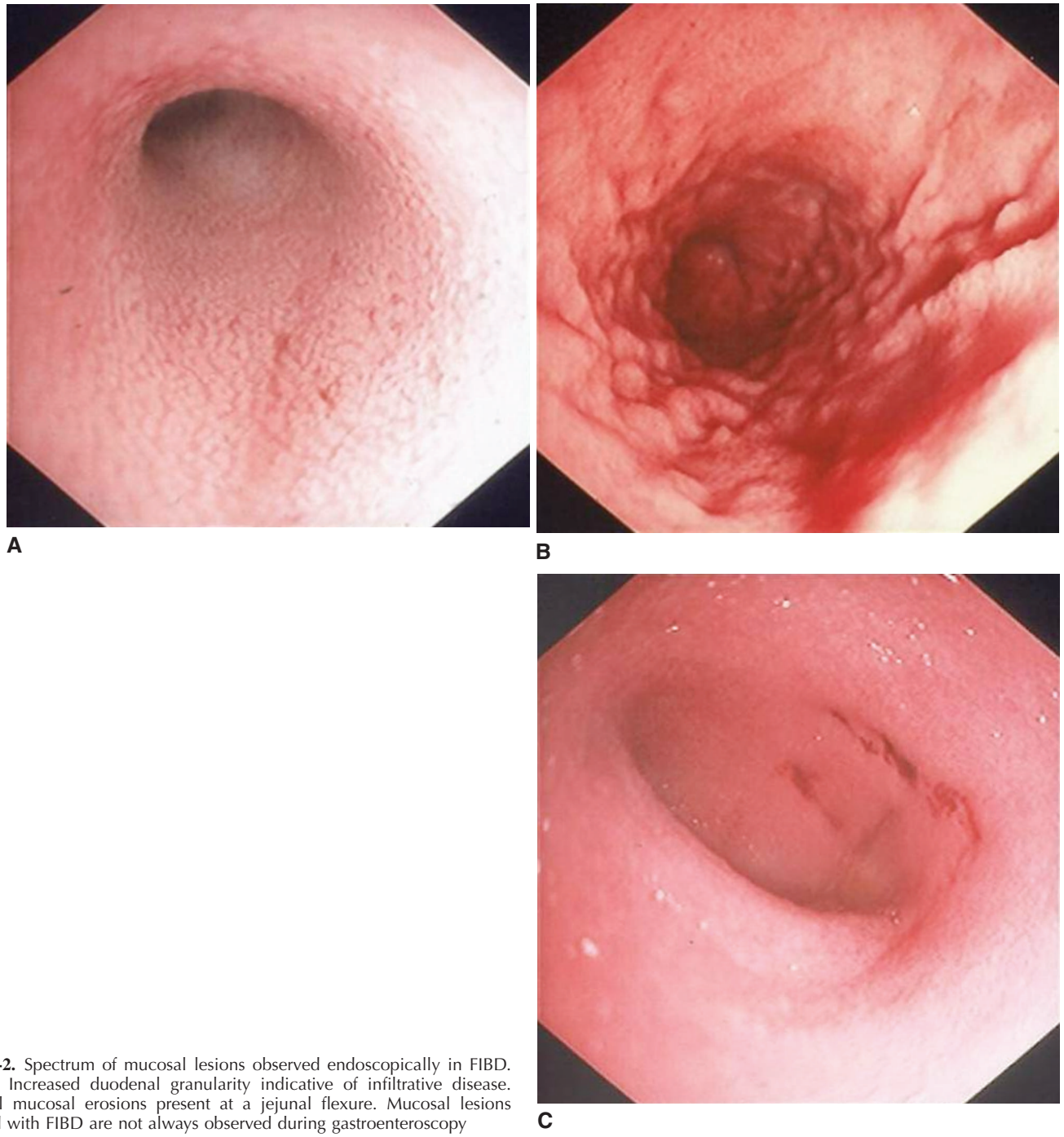

Figure 14-2. Spectrum of mucosal lesions observed endoscopically in FIBD. **A** and **B,** Increased duodenal granularity indicative of infiltrative disease. **C,** Several mucosal erosions present at a jejunal flexure. Mucosal lesions associated with FIBD are not always observed during gastroenteroscopy

epithelial alterations) in mucosal architecture.[21] Antibody reactivity to components of the normal endogenous bacterial flora also may contribute to the immunopathogenesis of chronic intestinal inflammation in cats with IBD.[22]

Summary of Current FIBD Indices

To date, clinical research investigations validate disturbances in mucosal immunity in cats with IBD. Unfortunately, only a few of these immunological parameters have been correlated to severity of clinical disease activity. Furthermore, the lack of consistent endoscopic abnormalities and the absence of standardized histological criteria for diagnosis of FIBD hinder use of these indices as reliable markers of intestinal inflammation. Recently, sonographic findings, including focal bowel wall thickening, loss of organized layer definition, and mesenteric lymphadenopathy, were shown to have relevance in staging FIBD.[23] However, the authors did not define the means by which severity of clinical signs was assessed. Given these limitations and previous experiences with human IBD indices, the use of gastrointestinal signs and simple parameters of inflammation (such as measurement of the acute phase response) would appear most appropriate for clinical assessment of FIBD activity.

Table 14-4 | **Clinical/Laboratory Summary of FIBD Activity Derived from the Largest Case-Based Studies Reported**

STUDY	CATS	CLINICAL SIGNS	LABORATORY	HISTOLOGY	DIAGNOSIS
Jergens et al (ref. 2)	26	Anorexia, V/D, weight loss, tenesmus	↓ albumin, ↑ TP, ↓ K^+, ↑ ALT	Graded	LPG/E/C Moderate
Dennis et al (ref. 12)	14	V/D, weight loss	↓ TP, ↓ K^+, ↓ albumin, ↑ ALT/ALP	Graded	LPG/E Varied per organ
Dennis et al (ref. 13)	14	Hematochezia, LB diarrhea	↓ K^+, ↑ ALT, ↓TP	Graded	LPC Severe
Hart et al (ref. 14)	60	Weight loss, V/D, anorexia	↑ TP, ↑ ALT/ALP	Graded	LPE/C Variable

V/D, Vomiting and diarrhea; *TP*, total protein; *K^+*, potassium; *LB*, large bowel diarrhea; *LPG/E/C*, lymphocytic-plasmacytic gastritis/enteritis/colitis; *LPC*, lymphocytic-plasmacytic colitis; *LPE/C*, lymphocytic-plasmacytic enteritis/colitis; *Graded*, denotes standardized histology scheme used; *ref*, reference.

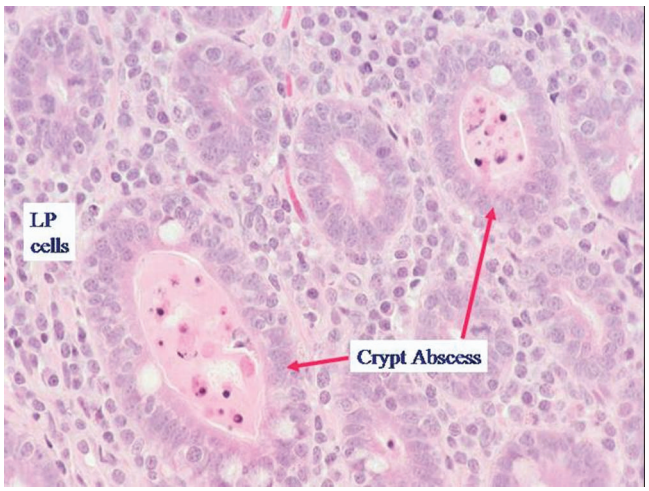

Figure 14-3. Histopathological appearance of severe lymphocytic-plasmacytic enteritis. Note the presence of marked lamina propria infiltrate of mononuclear cells and crypt abscessation, indicative of marked mucosal inflammation.

Table 14-5 | **Nine Independent Variables Evaluated Retrospectively for Potential Inclusion into a Proposed FIBD Activity Index**

VARIABLE	UNIT/CODE	CORRELATION*
GIT signs-anorexia	Yes/No	.088
Endoscopic lesions	Yes/No	.035
Total WBC	$\times 10^3/\mu l$	>.1
PCV	%	>.1
Total protein	gm/dl	.054
Albumin	gm/dl	>.1
ALT	IU/L	>.1
ALP	IU/L	.044
Phosphorus	mg/dl	.085

N = 62 cats.
*All variables correlated to histopathologic grade and expressed as a *P*-value.

Development of an FIBD Activity Index

Unfortunately, well-defined clinical criteria for assessment of feline IBD activity have not been published. This likely reflects the sparse number of studies reported and the inability of these authors to assess disease activity critically other than by severity of histological lesions.[2,12-14] Clearly themes emerge from these earlier investigations: (1) gastrointestinal signs of anorexia, weight loss, and vomiting predominate with gastric and/or small intestinal FIBD; (2) gastrointestinal signs of hematochezia, mucoid feces, tenesmus, and/or increased frequency of defecation are observed commonly with colonic IBD; (3) biochemical changes of altered plasma protein concentrations (e.g., hyperglobulinemia, hypoalbuminemia) and increased serum concentration of hepatic enzymes (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST], and/or alkaline phosphatase [ALP]) often are observed; and (4) histological lesions of lymphocytic-plasmacytic mucosal cellular infiltrates predominate (Table 14-4; Figure 14-4).

The first step in the development of an FIBD activity index may be the retrospective collection of a wide range of variables (e.g., prominent gastrointestinal signs and select laboratory parameters) and correlation of their association to severity of histological lesions. Once the optimal combination of variables is determined (via statistical analysis), this scoring formula should be evaluated rigorously and prospectively (preferably at multiple institutions) to assess its usefulness in a clinical setting. The advantages of the procedure described are (1) patient data from a single large-hospital population would be used (which would minimize interclinician variance experienced in the pilot study) and (2) this scoring index would be based on a somewhat balanced set of clinical and laboratory parameters.

Recently we completed a retrospective review of 62 cats diagnosed with FIBD over a 10-year period (1993-2003) at Iowa State University. FIBD was diagnosed on the basis of established clinical criteria[2,4] and histopathological lesions in endoscopic biopsy specimens. Because histology was considered the "gold standard" for diagnosis, stringent histological criteria of mucosal inflammation were used.[2,4,15,18] Patients who had concurrent diseases potentially causing nonspecific mucosal inflammation resulting from other causes (e.g., intestinal parasites, alimentary lymphoma, hyperthyroidism) were excluded from the study. These pilot data included those FIBD patients in which nine predictor variables for disease activity were identified. From these initial data, six variables were chosen for inclusion in the proposed scoring index on the basis of their statistical correlation to histopathological lesion score (Table 14-5). These predictor variables included (1) histology score; (2) presence of one or more chronic gastrointestinal signs; (3) total plasma protein concentration; (4) endoscopic mucosal abnormalities; (5) serum ALP; and (6) serum phosphorus concentration.

We presently are evaluating this proposed index in a multi-institutional prospective clinical trial. Initial FIBD clinical

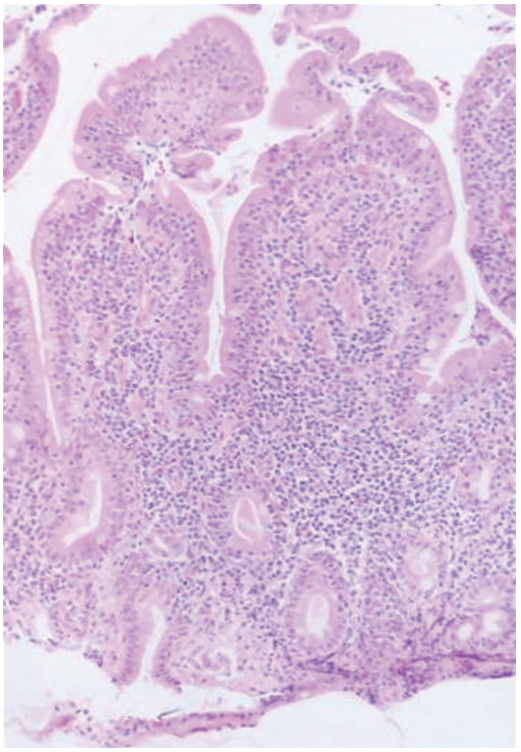

Figure 14-4. Histopathological appearance of an optimally oriented small intestinal biopsy specimen obtained endoscopically. Note the perpendicular orientation of the crypts and the depth of the biopsy specimen, which extends from the villi to the submucosa. The histological diagnosis in the cat was lymphocytic-plasmacytic enteritis.

scores will be recorded for each cat before endoscopy using the six standardized predictor variables as described previously. Concurrent with endoscopic examination, serum will be collected, divided into 200- to 500-µl aliquots, and stored at –70° C for later analysis of select acute phase proteins (APP). Serum APP, including acid glycoprotein (AGP) and serum amyloid A (SAA), will be assayed once the diagnosis is confirmed but before initiating medical therapy for FIBD. To establish whether medical therapy may influence inflammatory activity, FIBD clinical scoring and serum APP will be reevaluated in the IBD cats after 14 to 21 days of routine medical therapy (use of a restricted antigen diet coupled with administration of prednisone and/or metronidazole) for their disease.

Clinical Advantages and Limitations of an FIBD Activity Index

We expect to develop a simple clinical scoring system of the overall disease activity of FIBD. The proposed index should prove useful, because it is based on a well-balanced set of laboratory and clinical variables generated by statistical analysis of retrospectively collected data. Furthermore, this index encompasses a number of features deemed desirable in human IBD indices, including (1) it incorporates major gastrointestinal signs; (2) it uses observations that are apparent in-house; (3) it demonstrates visit-to-visit changes in disease activity; (4) it requires only simple calculation; (5) it should correlate with objective indices of disease activity; and (6) it should provide prognostic information of disease activity pre- and post-therapy.

One potential limitation of this project is that APP may not be altered in cats with IBD, either at the time of diagnosis or in response to medical therapy. However, our choice of AGP and SAA as surrogate markers of inflammation is based on observations (1) that SAA increases earliest in cats with inflammation, (2) that SAA and AGP in sera of hospitalized cats and cats with experimentally induced inflammation show good correlation in health and disease, and (3) that C-reactive protein (CRP) is not a highly responsive protein in the acute phase of cats, in contrast to human, equine, and canine CRP.[24] Alterations in acute phase proteins are not specific for gastrointestinal inflammation alone, and other concurrent inflammations and infections elsewhere in the body (causing an acute phase response) must be ruled out conclusively.[25,26] The primary value of altered acute phase proteins in evaluation of FIBD is as a component of the total assessment of the patient. Therefore it must be interpreted in conjunction with history, physical examination, radiologic, and histopathological findings.

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Chapter 15

Diarrhea in Kittens

Stanley L. Marks and Michael D. Willard

Diarrhea in kittens is one of the most common maladies facing the small animal clinician and managers of feline shelters and catteries.[1] A recent survey of the Association of Shelter Veterinarians identified kitten diarrhea as one of the top two concerns of veterinarians who treat shelter cats, second only to upper respiratory infections.[2] Clinical signs can range in severity from a mild, self-limiting diarrhea to a potentially fatal acute hemorrhagic diarrheal syndrome. Despite the significant clinical importance of diarrhea in kittens, veterinary literature does not provide much specific information on the causes and diagnosis of this malady. Antibiotics often are administered injudiciously to diarrheic kittens, and subsequent resolution of clinical signs often is equated wrongly with eradication of a "putative" infectious pathogen. Indiscriminate antibiotic therapy may even alter the commensal intestinal microflora, which leads to an exacerbation of the animal's diarrhea or development of antibiotic resistance.[3] Knowledge of the most common causes of diarrhea in kittens is integral to formulation of appropriate diagnostic and therapeutic plans and guidance for the veterinarian when standard therapeutic recommendations fail. Although diarrhea in kittens can be associated with a number of different etiologies, infectious causes are believed to play an important role in many of these cases.

PARASITIC CAUSES OF DIARRHEA

Trichomonosis

Tritrichomonas foetus, the primary causative agent of bovine trichomoniasis, recently has been recognized as a protozoal pathogen in cats (Figure 15-1).[4,5] In cattle, the obligate symbiotic protozoan is found primarily on the mucosal surface of urogenital cavities. It causes early embryonic death, abortion, and pyometra in infected cows.[6] Interestingly, *T. foetus* is found primarily on the large intestinal mucosal lining in cats.[4] Infected cats generally are young but have ranged in age from 3 months to 13 years of age (median 9 months). The pathogenicity of *T. foetus* for cats was demonstrated in a recent study in which eight cats were infected experimentally with a *T. foetus* strain isolated from a diarrheic kitten.[7] Trophozoites were cultured from the feces of all eight cats within 1 week after oral inoculation; infection persisted throughout the entire 203 days of the study, even when stools became normal.

Prevalence of T. foetus

The prevalence of *T. foetus* infection at an international cat show was found to be 31 per cent (36 out of 117 cats), with 28 out of 89 catteries affected.[5] Co-infection by *T. foetus* and *Giardia* spp. was common and was documented in 12 per cent of cats.

Misdiagnosis of *Giardia* spp. is common in cats with *T. foetus* infection. It may explain why cats diagnosed with apparent *Giardia spp.* infection do not respond to appropriate therapy. Risk factors for protozoal shedding and exacerbation of diarrhea included concurrent infection with *Cryptosporidium* spp., and cats living in close proximity with one another.[5] The predominance of infection in young cats from dense housing conditions may reflect an increased opportunity for exposure, or enhanced susceptibility to infection because of environmental stress or immunological immaturity.

Clinical Signs

T. foetus infection in cats can be associated with a chronic or recurrent large intestinal diarrhea characterized by increased mucus, tenesmus, occasional hematochezia, and increased frequency. The anus frequently is red, swollen, and painful, and fecal incontinence is not uncommon. Most cats usually are bright, alert, and responsive, and in good body condition with a normal appetite. *T. foetus* also can be cultured from the feces of asymptomatic cats, many of whom will not develop diarrhea.

Diagnosis

The following four methods of diagnosis should be considered in the order presented here.

MULTIPLE DIRECT FECAL SMEARS ON DIARRHEIC FECAL SPECIMENS. Direct fecal smears are indicated for the recovery of motile trophozoites of *Giardia* spp. and trichomonads such

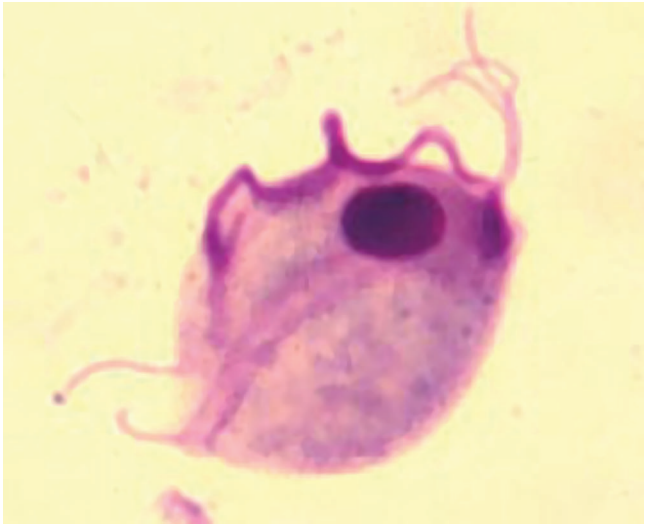

Figure 15-1. Giemsa-stained fecal smear showing characteristic appearance of *T. foetus* with its three anterior flagellae and long, undulating membrane.

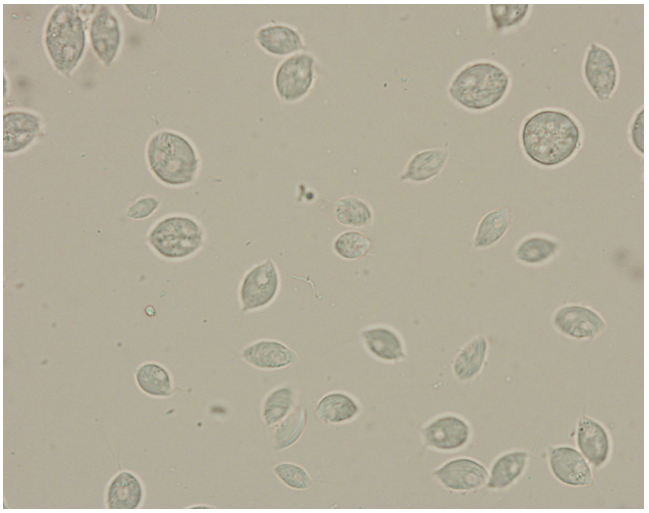

Figure 15-2. *T. foetus* trophozoites in culture medium (InPouch TF) isolated from a diarrheic cat (magnification ×400).

as *T. foetus*. The procedure should be performed with saline (0.9 per cent) and with use of fresh feces (body temperature, <2 hours old). Trophozoites in older specimens lose their motility and degenerate and become unrecognizable. The survival of trichomonads can be prolonged by adding 3 ml of 0.9 per cent saline to 2 g of feces. A small amount of feces is placed on a warm slide and a drop of 0.9 per cent saline is mixed with the feces. Alternatively, a miniscule amount of fresh feces can be collected by insertion of a cotton-tipped swab into the rectum. The smear must not be too thick, because trophozoites will be missed easily. A simple rule of thumb is that the observer should be able to read the fine newsprint of a newspaper through the smear.

After application of a coverslip, the smear is evaluated for motile organisms by examining at 10× magnification, with confirmation at 40× magnification. After the wet preparation has been checked thoroughly for motile trophozoites, a drop of D'Antoni's iodine can be placed at the edge of the coverslip, or a new wet mount can be prepared with iodine alone for morphological identification of the organism. A weak iodine solution that resembles "strong tea" is recommended.

The main limitation of direct fecal smears is sample size, with the result that negative smears are not uncommon with low parasite burdens. The sensitivity of direct fecal smear examination for diagnosis of *T. foetus* is relatively low in cats with spontaneous disease (14 per cent).[8] In addition, *T. foetus* can be difficult to distinguish from nonpathogenic intestinal trichomonads such as *Pentatrichomonas hominis* using light microscopy. *T. foetus* should be distinguished from *Giardia* spp. *Giardia* trophozoites have a concave ventral disc, and motility that mimics a falling leaf. In contrast, trichomonads are spindle-shaped, have an undulating membrane that courses the entire length of the body, and move in a more irregular and jerky fashion. In contrast to *Giardia* spp., trichomonads do not have a cyst stage, which underscores the limitations of fecal flotation technique for diagnosis of trichomoniasis. *Trichomonads will not survive refrigeration and are found rarely in formed fecal specimens*.

FECAL CULTURES PERFORMED WITH AN INPOUCH TF KIT. A commercially available system marketed for diagnosis of *T. foetus* infection in cattle (InPouch TF, Biomed Diagnostics, White City, OR) should be considered if multiple direct fecal smears are negative for trophozoites.[8] Approximately 0.05 g (less than a peppercorn) of freshly voided feces can be placed in the InPouch for culture, or alternatively, a saline-moistened cotton-tipped swab can be placed in the rectum and then gently agitated in the InPouch for culture. The InPouch should be incubated at room temperature in an upright position in the dark and examined every 48 hours for up to 12 days for motile trophozoites with use of a 20× or 40× objective (Figure 15-2). Before microscopic evaluation, it is easiest to place the pouch in a plastic clamp provided by the manufacturer that facilitates mounting of the pouch onto the stage of a light microscope. The media in the pouch does not support the growth of *Giardia* spp. or *Pentatrichomonas hominis*, although further studies to evaluate the specificity of the InPouch are warranted.

SINGLE TUBE-NESTED PCR OF DNA EXTRACTED FROM FECES. A sensitive and specific single-tube nested PCR based on amplification of a conserved portion of the *T. foetus* internal transcribed spacer region (ITS1 and ITS2) and 5.8 rRNA gene from feline feces has been described.[9] The PCR test is more sensitive than fecal culture and tested positive in 55 per cent of cultures that were negative for *T. foetus*, even when feces were normal.

COLONIC MUCOSAL BIOPSY. Colonic mucosal biopsies are advocated once the above mentioned diagnostics have been completed. Histopathological changes in colonic mucosal biopsies from infected cats have consisted predominantly of a lymphocytic and plasmacytic infiltrate with a significant neutrophilic component. The intestinal epithelium frequently is attenuated, and immunohistochemistry has been used to detect the trichomonads on the surface epithelium and within crypts.

Therapy

No therapy currently exists for elimination of *T. foetus*, and cats infected with *T. foetus* have failed treatment with recommended

and higher dosages of numerous antimicrobial drugs, including metronidazole, fenbendazole, sulfadimethoxine, furazolidone, tylosin, amoxicillin, and paromomycin.[4] Despite their failure to eradicate infection, some cats do show a mild improvement in fecal consistency while receiving antimicrobial drugs. This may reflect an alteration of the endogenous intestinal microflora that supports the trichomonads, or effective resolution of cofactors (*Giardia* spp., *Cryptosporidia* spp., other coccidia), that could exacerbate the cats' diarrhea. Prolonged use of antimicrobials has not been successful for long-term control of diarrhea and may delay the onset of clinical remission or exacerbate the diarrhea in some animals. In addition, higher doses of certain antibiotics such as metronidazole and paramomycin may cause adverse effects in cats, including neurotoxicity and nephrotoxicity,[10] respectively. A recent report showed that more than 50 per cent of cats diagnosed with *T. foetus*–associated diarrhea were still shedding the organism up to 5 years after diagnosis based on PCR confirmation, and diarrhea persisted for up to 3 years in many cats, despite aggressive antimicrobial administration.[11] Relapses of diarrhea were common and associated with dietary change, medical treatments unassociated with *T. foetus* infection, and travel.[11] Currently, it is unknown whether long-term infection of cats with *T. foetus* is a predisposing factor for development of inflammatory bowel disease. In light of the poor host specificity of *T. foetus* and the intimate association between infected cats and their human companions, the potential for zoonotic transmission should be considered. A single case of human infection with *T. foetus* has been documented in the literature to date. In that case, the infection presented as epididymitis and meningoencephalitis after immunosuppression and peripheral blood stem cell transplantation.[12]

Cryptosporidium Species

Coccidia of the genus *Cryptosporidium* spp. are small, ubiquitous protozoan parasites that replicate in the microvillous borders of intestinal and respiratory epithelium of many vertebrates, including birds, mammals, reptiles, and fish.[13]

Clinical Signs

Infection with *Cryptosporidium parvum* in kittens and immunosuppressed cats causes a spectrum of disease ranging from asymptomatic carrier state to mild, transient diarrhea, cholera-like illness, or prolonged, life-threatening malabsorption syndrome.[14] The organism also has been associated with diarrhea in adult cats without obvious evidence of immunosuppression.[15] In addition, *C. parvum* infection has been diagnosed in association with intestinal cellular infiltrates indistinguishable from those seen with inflammatory bowel disease in cats.[15] Caution should be heeded in overinterpretation of the presence of the organism with these infiltrates, because other co-factors, including diet, may have been associated with these cellular infiltrates.

Diagnosis

Despite the relatively high seroprevalence rates of *C. parvum*–specific IgG in cats (8.3 to 87 per cent),[16-18] the laboratory detection of this ubiquitous protozoan parasite in spontaneously infected diarrheic cats is difficult, predominantly because the organism is so small (average 4.6 × 4.0 μm) and difficult to find in fecal specimens via light microscopy[19] and because fecal shedding may be intermittent. Current laboratory protocols for detection of *Cryptosporidium* oocysts in fecal specimens include microscopic examination of smears stained with Giemsa, the modified Ziehl-Neelsen technique (Figure 15-3), the modified Kinyoun acid-fast technique, or use of an immunofluorescent detection procedure (Figure 15-4).[20,21] Immunofluorescent detection procedures are more sensitive and specific than acid-fast stains and generally are the method of choice for morphological diagnosis in human beings.[22] Microscopic techniques work well when clinical signs are present and oocyst numbers are relatively high; however, once clinical signs abate and oocyst numbers are greatly decreased, the sensitivity of tests relying on morphological identification is reduced and diagnosis often requires examination of multiple fecal specimens. In these cases, the newer enzyme immunoassays designed to detect *Cryptosporidium* spp. antigens in feces have proven more sensitive.[23] Difficulties in detection and enumeration of oocysts in fecal specimens are compounded by variation in consistency between individual fecal specimens, the amount of specimen used, and oocyst losses incurred during recovery processes. Although several diagnostic tests have come into widespread general use, the veterinary literature lacks published data that compare different diagnostic methods in cats. No single procedure has become adopted universally.

A recent study compared the performance characteristics of a Ziehl-Neelsen stain, direct fluorescent antibody technique, and three ELISA tests* (Table 15-1).[21] It revealed that the ProSpecT Microplate ELISA was the most sensitive diagnostic test for *Cryptosporidium* spp. on a single day, whereas the ProSpecT Rapid ELISA was highly insensitive and should not be used by veterinary diagnostic laboratories.

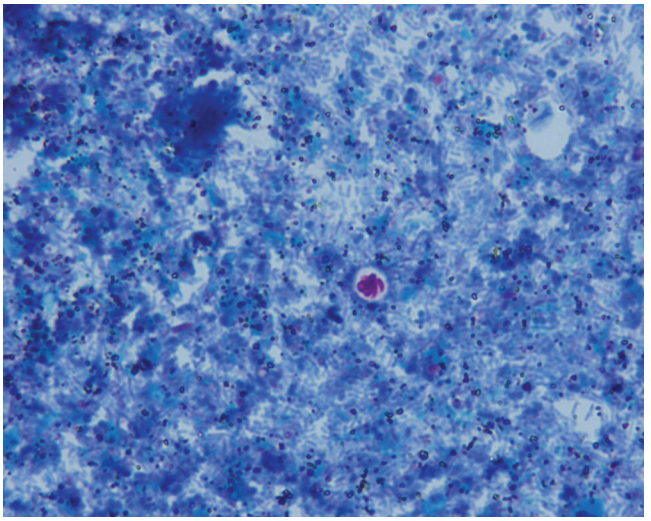

Figure 15-3. Fecal smear showing a single acid-fast (modified Ziehl-Neelsen) staining *Cryptosporidium* oocyst from a diarrheic cat (magnification ×1000).

*Premier Cryptosporidium ELISA, Meridian Biosciences Inc., Cincinnati, OH; Remel ProSpecT Microplate ELISA, Lenexa, KS; and Remel ProSpecT Cryptosporidium Rapid ELISA.

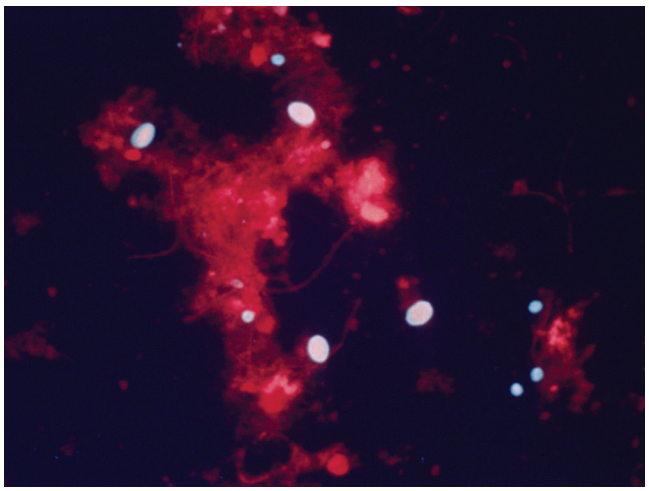

Figure 15-4. Direct immunofluorescent assay (Merifluor *Cryptosporidium/Giardia* direct immunofluorescent kit, Meridian Diagnostics Inc, Cincinnati, OH) showing fluorescent *Giardia* cysts (larger, oval) and *Cryptosporidium* oocysts (smaller, round).

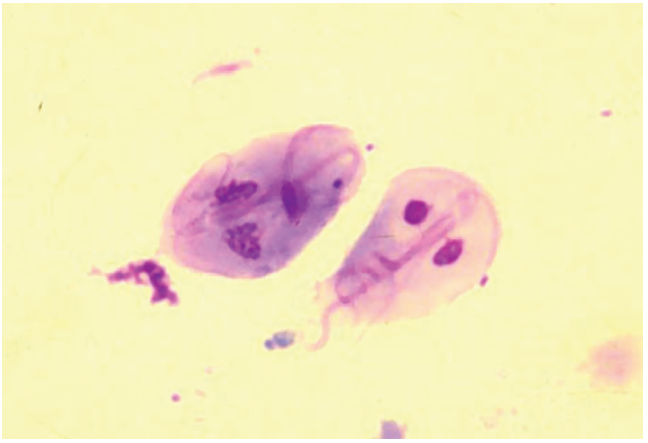

Figure 15-5. Giemsa-stained fecal smear showing two *Giardia* trophozoites exhibiting the characteristic pear, or teardrop, shape with bilateral symmetry when viewed from the top, two nuclei, and fibrils running the length of the parasite.

Table 15-1 | **Cumulative Sensitivities of Five Methods of Detection of *Cryptosporidium* Species in Fecal Specimens Collected Once Daily over 4 Consecutive Days from 104 Naturally Exposed Kittens**

DETECTION METHOD	DAY 1	DAY 3	DAY 4
Ziehl-Neelsen technique	72%	91%	94%
Direct immunofluorescence detection	50%	83%	84%
Meridian Premier ELISA	80%	93%	93%
Remel ProSpecT Microplate ELISA	89%	94%	95%
Remel ProSpecT Rapid ELISA	15%	43%	49%

Treatment

Eradication of this parasite has proven difficult, and many putatively effective drugs are either toxic or ineffective in cats. The aminoglycoside, paromomycin, is potentially nephrotoxic[10] and ototoxic in cats and preferably should not be used. Although the benzamide antimicrobial, nitazoxanide, has been shown to eradicate *Cryptosporidium* spp. in human beings and cats, its administration to cats was associated with unacceptable adverse effects (i.e., vomiting and anorexia). One report stated that tylosin was effective in eradicating *Cryptosporidium* infection in a cat[15]; however, I* recently completed a prospective double-blind study that failed to show any benefit for tylosin in naturally infected cats. Azithromycin is used in human beings for management of cryptosporidiosis and appears safe in cats when administered at a dosage of 7 to 10 mg/kg PO q12h for 7 days; however, the efficacy of this treatment in cats is unknown.

Giardia Species

Giardia spp. are an important cause of outbreaks of waterborne infection resulting from contamination of raw municipal water, back-country streams, and lakes with human effluent or infected animal feces.[24] The overall prevalence of *Giardia* spp. infection in cats in North America has been reported at about 4 per cent, with much higher levels in kittens and in cats housed in shelters.[25]

Clinical Signs

Giardia infections in adult cats often are subclinical or associated with a transient softening of the stool early in the infection; however, acute diarrhea tends to occur in kittens shortly after infection. Feces are often malodorous, pale, and may contain mucus.

Diagnosis

The diagnosis of *Giardia* infection traditionally has depended on microscopic identification of trophozoites (Figure 15-5) or cysts (Figure 15-6) in feces from affected animals. However, microscopic diagnosis of *Giardia* infection can be difficult, because (1) cysts may be shed intermittently and (2) they are so delicate. Many artifacts (e.g., grass pollen, yeast) mimic the morphology of *Giardia* cysts to varying degrees, and care must be exercised in differentiating these from *Giardia* spp. A recent survey evaluated the sensitivity of fecal flotation for detection of *Giardia* spp. in dogs and confirmed the poor performance of current in-house microscopy testing for *Giardia* spp. compared with microplate ELISA. In that study, microscopy following fecal flotation identified only half of the infected dogs and falsely diagnosed up to 25 per cent of uninfected animals.[26]

Accurate identification of these parasites in diarrheic cats is important because the organism could be a zoonosis[27] and failure to detect these parasites in diarrheic cats often leads to injudicious antibiotic therapy, which can exacerbate the diarrhea. Many veterinarians and reference laboratories have resorted to using ELISA tests that rely upon detection of *Giardia* cyst wall protein I (GCWP 1).[28] The ELISA tests are advantageous because they are generally easy to perform and results are easy to interpret. In addition, the test does not rely upon morphological identification of cysts or oocysts via

*One of the chapter co-authors, Stanley L. Marks.

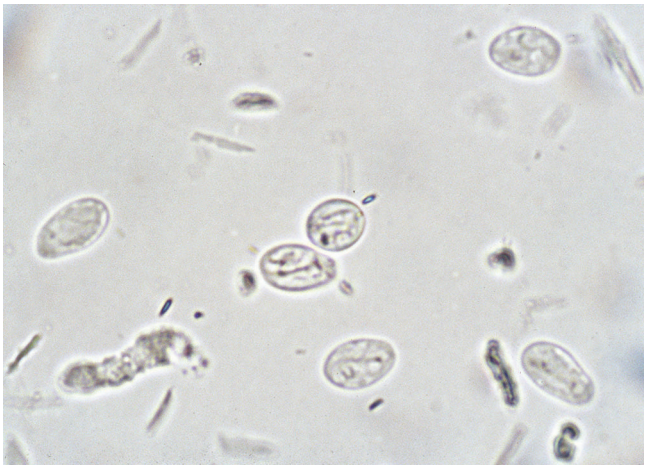

Figure 15-6. Zinc sulfate fecal flotation showing *Giardia* cysts with distinctive fibrils (axonemes) coursing the length of the cyst (magnification ×400).

microscopy, which saves technician time and potentially avoids false-negative interpretations. The ELISA tests also can detect GCWP 1 in the absence of detectable cysts.[28] However, virtually every commercially available ELISA is marketed for human use, and studies are few that appraise their performance characteristics in diarrheic cats and dogs.

Recently, a novel SNAP *Giardia* Test Kit (IDEXX Laboratories, Inc., Westbrook, Maine) for detection of GCWP 1 in canine and feline feces was released. The SNAP *Giardia* Test is a rapid in-house enzyme immunoassay that can be performed on fresh feces, previously frozen feces, or feces stored at 2 to 7° C for up to 7 days. This test represents the first commercially available ELISA designed specifically for dogs and cats and has the added advantages of simplicity, rapid availability of results (8 minutes after mixing of the conjugate solution with feces), and low cost. The performance characteristics of this test have not been well characterized; the test must be scrutinized against the performance characteristics of other ELISAs, fecal flotation, and the immunofluorescence assay. Preliminary studies in our laboratory found a relatively high sensitivity (86 per cent) for the Remel ProSpecT Microplate ELISA in cats naturally infected with Giardia spp., whereas the Remel ProSpecT Rapid ELISA had an unacceptably low sensitivity of 56 per cent.[29] Immunofluorescence detection procedures (see Figure 15-4) are more sensitive and specific than acid-fast stains and generally are the method of choice for morphological diagnosis of cryptosporidiosis in human beings.[22]

Treatment

Metronidazole was shown to be highly effective and safe when given at 25 mg/kg PO q12h for 7 days to cats with experimental infections.[30] Albendazole also is relatively effective when dosed at 25 mg/kg PO q12h for 5 days; however, the drug has been associated with pancytopenia and is teratogenic. A recent trial evaluating the efficacy of fenbendazole in cats co-infected with *C. parvum* revealed that the drug was safe; however, it was relatively ineffective (50 per cent).[31] Additional studies with this drug are warranted in cats with *Giardia* spp. and lack of co-infection. Drontal Plus was shown to be relatively safe and effective in experimentally infected kittens when given at twice the recommended dose. The dose of febantel used was 56.5 mg/kg PO.[32]

Control of Giardia *Infection*

The following four fundamental steps should be taken to control *Giardia* infection and minimize reinfection of treated animals:

1. The environment is decontaminated. Simultaneous treatment of animals with the medications and decontamination of the environment with a quaternary ammonium-based (QUAT) disinfectant (Roccal D, Totil, Quatsyl 256, or Aqua Quat 400) should improve effectiveness of treatment and maximize the possibility of eliminating *Giardia* spp. from the cattery or shelter. Specifically, gross fecal contamination should be removed as much as possible on a daily basis. Runs should be rinsed with water, after which a layer of disinfectant foam (Roccal D) should be applied. After 10 to 20 minutes, the foam should be rinsed away with fresh water. Cages should be sponged clean on a daily basis with a dilute disinfectant or mix of Clorox diluted at 1:32 and Quatsyl 256 at 1:256.[33]
2. The animal is treated with effective drugs.
3. The animal is bathed to clean cysts from the coat.
4. Reintroduction of infection is prevented.

Giardia *Vaccine*

A commercial *Giardia* vaccine (GiardiaVax, Fort Dodge Animal Health, Overland Park, KS) with chemically inactivated trophozoites has been prepared and licensed for use in cats in the United States. Efficacy studies conducted in kittens revealed that fewer vaccinated animals developed diarrhea after oral challenge, and diarrhea in vaccinated animals was of short duration compared with controls. Vaccination also reduced the duration of cyst shedding and the number of cysts shed in the feces when compared with control animals.[34] The administration of three doses of GiardiaVax as an immunotherapy to experimentally infected kittens was ineffective in eradicating cysts.[35] We do not advocate the routine vaccination for *Giardia* spp. in household cats.

Coccidia Species

Cats are infected with two species of coccidia, *Isospora rivolta* and *Isospora felis* (Figure 15-7). Immunity to *I. rivolta* is not complete, and some oocysts are shed after challenge.[36] Kittens that are 4 weeks old are most susceptible to infection with *I. felis*. Enteritis, emaciation, and death can occur after inoculation of 10^5 oocysts.[37] Studies indicate that cats infected naturally with *I. felis* develop lower antibody titers than do those inoculated experimentally with *I. felis*.[38]

Diagnosis

Fecal flotation with zinc sulfate is the recommended method. Examination of stools for bacterial and viral agents that cause disease in these animals is important because coccidiosis usually is asymptomatic. Cats can have oocysts in their fecal

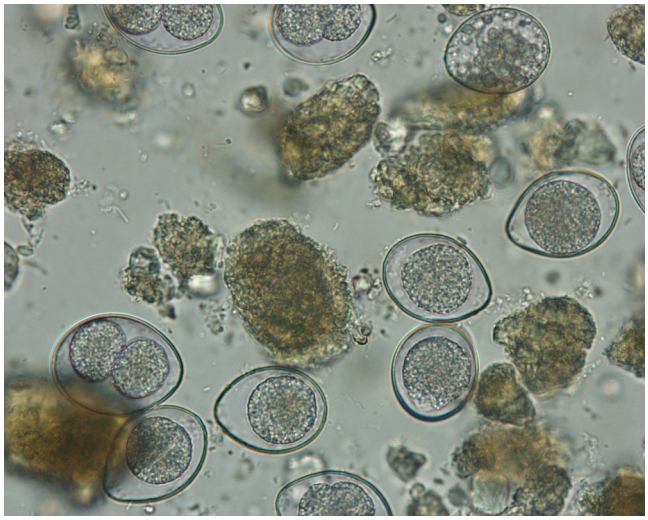

Figure 15-7. Zinc sulfate fecal flotation showing *Isospora* spp. oocysts recovered from a diarrheic kitten (magnification ×400).

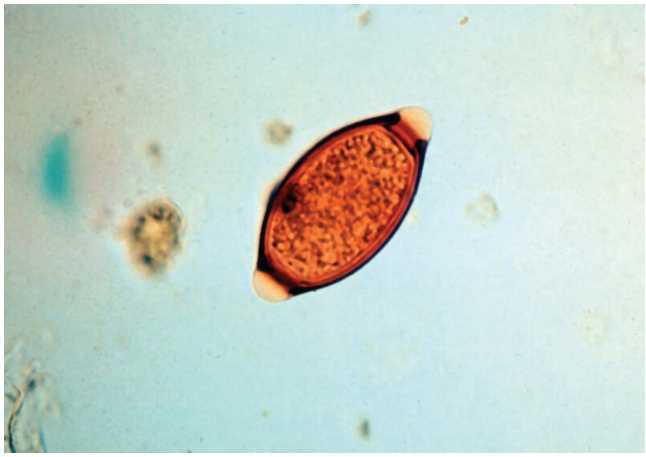

Figure 15-8. Fecal flotation showing biperculate *T. vulpis* ovum (magnification ×400).

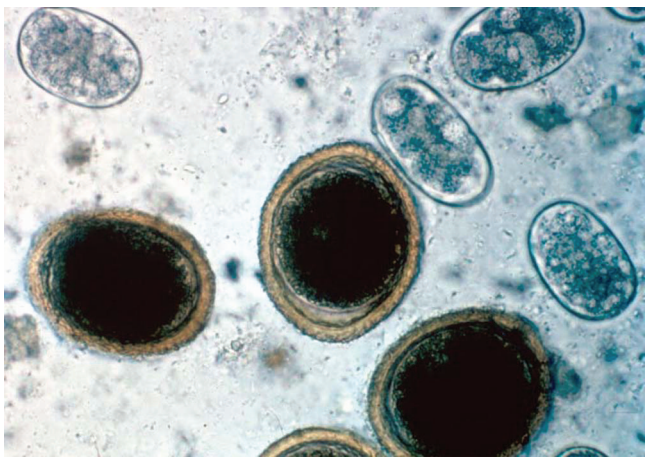

Figure 15-9. Fecal flotation showing large, thick-walled ova of *T. cati* and *Ancylostoma caninum* ova (magnification ×400).

specimens from ingestion of prey. These should be recognized as pseudoparasites. The most common of these are *Eimeria* species from ruminants, rabbits, or rodents. These oocysts will not be in the two-celled stage as is common for *Isospora* species. They often have ornamentations such as micropyle caps or dark thick walls that are not found on *Isospora* oocysts.

Treatment

Sulfadimethoxine given at 50 mg/kg PO q24h for 10 to 14 days eliminates oocyst excretion in most cats.[39] The combination of ormetoprim (11 mg/kg) and sulfadimethoxine (55 mg/kg) given orally for up to 23 days has been used effectively in dogs. Amprolium given at 300 to 400 mg/kg PO q24h for 5 days, or 110 to 220 mg/kg PO q24h for 7 to 12 days, is effective in treatment of coccidiosis in dogs. Other agents such as furazolidone, quinacrine, and metronidazole probably are of little clinical value.

Whipworms

Cats rarely acquire whipworm infections, although they are a possibility in animals with clinical signs of colitis. The adult worms burrow into the colonic and cecal mucosa and may cause inflammation, hematochezia, and intestinal protein loss.

Diagnosis

T. vulpis should be considered in animals with evidence of colonic disease. A fecal centrifugation flotation should allow recognition of the biperculate ova (Figure 15-8). However, intermittent shedding has been well documented in dogs; therefore cats with a negative fecal flotation should be dewormed empirically.

Treatment

Fenbendazole is a safe broad-spectrum anthelminthic. The drug is administered orally at 50 mg/kg q24h for 5 consecutive days, and the regimen is repeated at 3 weeks and 3 months after initiation of therapy.

Roundworms

Roundworms are common in cats (*Toxocara cati* and *Toxascaris leonina*) and can cause diarrhea, failure to thrive, a poor haircoat, and a "potbellied" appearance. Vomiting is observed occasionally when the roundworms gain access to the stomach.

Diagnosis

The large ova (approximately 80 µm) with a characteristic thick wall are easy to recognize on fecal flotation (Figure 15-9).

Treatment

Pyrantel at 20 mg/kg PO is safe in kittens. The treatment should be repeated at approximately 3 weeks. Fenbendazole also is an effective anthelminthic and can be administered to newborn kittens at 50 mg/kg PO for 3 days to kill more than 90 per cent of prenatal larvae. Kittens should be dewormed routinely every 2 weeks, starting at 2 weeks of age, until 8 weeks.

Hookworms

Cats are infected with *Ancylostoma tubaeforme*, *Ancylostoma braziliense*, *Uncinaria stenocephala*, and less commonly, the canine hookworm, *Ancylostoma caninum*. The worms are voracious blood suckers and attach to the mucosa of the small intestine. Hookworm infections in cats are relatively uncommon with reported prevalences of 0.9 and 1.1 per cent.[40] Kittens are infected by ova ingestion or through transcolostral transmission. Kittens occasionally can have life-threatening blood loss or iron-deficiency anemia, melena, hematochezia, and failure to thrive.

Diagnosis

Fecal flotation should be positive because the worms produce a large amount of eggs (see Figure 15-9).

Treatment

Fenbendazole and pyrantel are effective in cats.

MAXIMIZING THE DIAGNOSTIC YIELD OF A FECAL EXAMINATION

A fecal examination is integral to the diagnostic work-up of kittens with diarrhea, vomiting, and weight loss. The techniques used most commonly include direct fecal smear (wet prep), stained smear, and a fecal flotation. A Baermann technique is indicated when parasitic larval stages are being evaluated.

Stained Smear

Traditionally, stained smears have been examined to evaluate for the presence of endospores associated with *Clostridium perfringens*; for the presence of spiral-shaped, gram-negative bacteria consistent with *Campylobacter* spp.; or, for the presence of increased white blood cells. The diagnostic value of finding increased fecal endospores (Figure 15-10) is virtually zero, because healthy, nondiarrheic cats and dogs also can have increased fecal endospores. In addition, no correlation exists between increased fecal endospores and the presence of fecal enterotoxin. Finding spiral-shaped bacterial organisms should be interpreted with caution because many *Campylobacter* spp. are found in cats, and many are nonpathogenic. Perhaps the best use of stained fecal smears is to make a diagnosis of intestinal lymphoma, and intestinal *Histoplasma* or *Prototheca* infections, the latter two of which are rare in cats. The diagnostic yield of stained fecal smears can be increased by use of a cotton swab introduced into the rectum and rotated gently several times. The cotton swab is rolled onto a glass slide, which is then stained after air drying.

Fecal Flotation

Fecal flotations are indicated to find cysts, oocysts, and ova in feces. Fresh feces should be examined whenever possible, or a fresh specimen can be refrigerated for up to 72 hours for detection of cysts, oocysts, or eggs via a concentration technique. Fresh feces also can be placed in 10 per cent buffered formalin if evaluation will be delayed more than 72 hours. Specimens

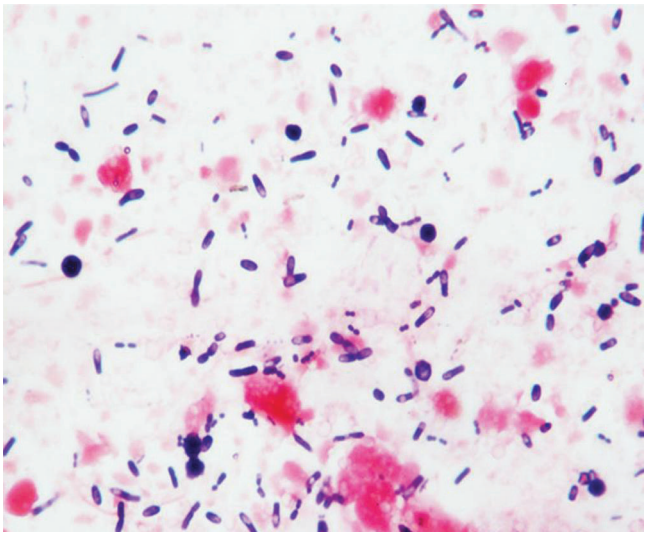

Figure 15-10. Stained fecal smear (modified Wright's stain) from a healthy, non-diarrheic cat showing numerous endospores of *C. perfringens* (magnification ×1000)

Figure 15-11. Centrifuge with free swinging buckets showing a coverslip in place before centrifugation.

fixed in formalin are suitable for concentration techniques, acid-fast stains, and immunoassays. Although standing (gravitational) flotation methods are easier and quicker to perform than centrifugation flotation (Figure 15-11), the latter clearly has superior sensitivity (up to eight times).[41] Animals with low parasite burdens could have a false-negative result if the gravitational method is used. Fecal flotations have limitations and should not be used to detect heavy ova that do not float (*Paragonimus* spp.) or larvae (*Aelurostronglyus* spp.).

The type of flotation medium used and specific gravity of flotation medium are important considerations. We recommend zinc sulfate with a specific gravity of 1.18 or 1.2 for flotations. This solution and specific gravity are optimal for flotation of ova and *Giardia* cysts, while the structural detail of the *Giardia* cyst is maintained.

Procedure for Centrifugal Flotation

1. A fecal emulsion is prepared with use of 2 to 5 g of feces and 5 to 10 ml of flotation solution.

2. The emulsion is strained through a tea strainer or cheesecloth with 10- to 15-ml flotation solution into a 15- to 20-ml conical centrifuge tube.
3. The tube is filled with flotation medium to create a positive meniscus.
4. A coverslip is placed on top of the tube.
5. The tube is balanced in the centrifuge.
6. The tubes are centrifuged for 10 minutes at 1500 to 2000 rpm.
7. The coverslips are removed carefully from the tubes by lifting straight up; they are placed on a clean slide.
8. The slide is examined within 10 minutes. The entire coverslip is examined at 10×. A magnification of 40× is used to confirm identification by visualizing internal structures and measuring the organism.

Modification

With a centrifuge that is fixed-angle and does not have free swinging buckets, the above procedure should be followed but the centrifuge tube is filled to within an inch or so from the top, and a coverslip is not added for the final spin. When the final centrifugation step is complete, the tube is set upright carefully in a test tube rack. A pipette is used to gently run additional flotation solution down the side of the tube while disturbing the contents as little possible. A positive meniscus is created and a coverslip set on top. This preparation should be allowed to stand for 5 minutes only. The coverslip is removed to a slide and examined as described in step 8.

BACTERIAL CAUSES OF DIARRHEA

Diagnosis of bacterial-associated diarrhea in kittens is difficult for two reasons: (1) the isolation rates for putative bacterial enteropathogens often are similar in diarrheic and nondiarrheic animals and (2) the incidence of bacterial-associated diarrhea is extremely variable. Caution should be heeded in interpretation of the results of fecal ELISAs for *C. perfringens* enterotoxin (CPE) and *C. difficile* toxin A and/or B in neonatal kittens because of the high incidence of positive ELISAs (up to 50 per cent) I* documented in apparently healthy kittens. The effects of *C. difficile* toxin A and B have been shown to be dependent on age in human beings and dogs, in whom high levels of toxins are detected in the feces of neonates in the absence of clinical signs of disease.[42,43] The reader is referred to Chapter 5 for a more detailed description of specific bacterial enteropathogens associated with diarrhea.

The indications for performance of fecal enteric panels on diarrheic kittens are poorly defined, which results in indiscriminate testing and misinterpretation of results. Fecal cultures and toxin analysis for specific bacteria should be reserved for (1) kittens that develop diarrhea after kenneling or show attendance once parasitic causes for diarrhea have been ruled out, (2) kittens with an acute onset of bloody diarrhea in association with evidence of sepsis, (3) outbreaks of diarrhea occurring in more than one household pet, and (4) screening for enteropathogens (*C. difficile*, *Campylobacter* spp., or *Salmonella* spp.) when zoonotic concerns are present. A recently published study documented the prevalence of five groups of potentially zoonotic enteric infections (*Salmonella* spp., *Campylobacter* spp., *Cryptosporidium* spp., *Giardia* spp., and *Toxocara cati*) in fecal samples from cats under 1 year of age that were either housed in humane shelters or presented to primary-care veterinarians in central New York State[44] (see Chapter 75). Possible associations of these organisms with the cat's source or with the presence of diarrhea were evaluated. The proportion of fecal samples with one or more zoonotic organisms was 35.1 per cent among client-owned cats and 44.2 per cent among shelter cats. The prevalence of *Salmonella* spp. was 0.8 per cent, which is similar to the reported prevalence of *Salmonella* spp. in cats in Colorado[27] and in kittens from shelters in Japan (1.1 per cent).[45] I* also have documented a relatively high incidence of *Campylobacter* spp. in fecal specimens from nondiarrheic cats and kittens (approximately 20 per cent).

Miscellaneous Bacterial Causes of Diarrhea

Anaerobiospirillum *Species*

Anaerobiospirillum spp. are motile, spiral-shaped, anaerobic gram-negative rods that were first identified by Malnick and coworkers (1983) in two human patients with diarrhea.[46] Since then, *Anaerobiospirillum succiniciproducens* and *Anaerobiospirillum thomasii* have been recognized as causes of septicemia, particularly in immunocompromised human beings, and have been isolated from the throat and feces of healthy cats and dogs.[47,48] We have identified three cats with clinical signs of acute onset of vomiting, diarrhea, and abdominal pain that progressed rapidly to systemic disease characterized by lethargy and collapse. On necropsy, an acute to subacute ileocolitis was found in association with abundant spiral-shaped organisms confirmed as *Anaerobiospirillum* spp.[49] (Figure 15-12).

Anaerobiospirillum spp. and *Campylobacter* spp. are similar morphologically and can be confused. *Anaerobiospirillum* spp. are oxidase and catalase negative, whereas *Campylobacter* spp. usually are oxidase and catalase positive. *Anaerobiospirillum* spp. demonstrate corkscrew motility, whereas *Campylobacter* spp. display darting motility. *Anaerobiospirillum* spp. have bipolar tufts of flagella, whereas *Campylobacter* spp. have a single flagellum on one or both poles. Although the organisms have been isolated from the rectal swabs of asymptomatic dogs and cats, they have not been isolated from the feces of asymptomatic human beings. Most human patients infected with *Anaerobiospirillum* spp. are immunocompromised, and the organism is a rare cause of bacteremia in people. According to the NCCLS breakpoints for anaerobes, the isolates are susceptible to amoxicillin-clavulanic acid, cefoxitin, imipenem, and penicillin, intermediately susceptible to metronidazole, and resistant to clindamycin.

Helicobacter *Species*

Helicobacter spp. are gram-negative, microaerophilic spiral-shaped, motile bacteria that colonize the gastrointestinal tract of several mammalian and avian hosts. Because inflammatory bowel disease (IBD) is a common clinical finding in domestic cats, and because *Helicobacter* spp. are associated with IBD in mice and rats, the possible relationship between helicobacters

*One of the chapter co-authors, Stanley L. Marks.

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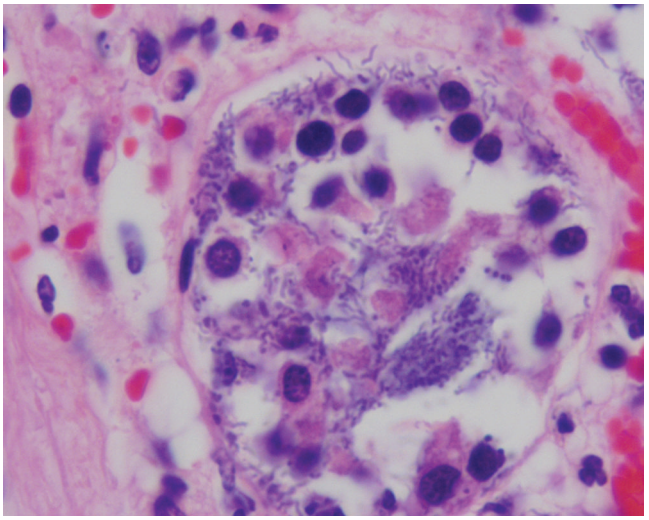

Figure 15-12. Light photomicrograph of colon obtained from a cat, showing spiral-shaped *Anaerobiospirillum* bacteria inside the lumen of a dilated crypt (Steiner stain) (magnification ×1200).

and IBD in cats should be explored. *Helicobacter canis* was isolated from four Bengal cats with and without chronic diarrhea.[50] Because the cats were coinfected with other potential pathogens, including *Campylobacter helveticus*, and because *H. canis* was isolated from nondiarrheic cats, the causal role of *H. canis* in production of the diarrhea could not be proven.[50] Histologically, the colons of the four affected cats were characterized by mild to moderate neutrophilic, plasmacytic, and histiocytic infiltrates in the lamina propria, with crypt abscesses.

A 4-month-old male British blue cat with catarrhal to hemorrhagic enteritis showed massive colonization of the stomach, small intestine, and cecum with spiral-shaped bacilli that strongly resembled *Flexispira rappini*, a spiral-shaped *Helicobacter* species known as a normal intestinal colonizer in dogs and mice.[51] Inflammatory infiltration was moderate and T-cell dominated. In the intestine, bacilli were found in the gut lumen, between villi, in crypt lumina, and within epithelial cells. Degeneration of crypt epithelial cells was observed, in addition to crypt dilation and moderate to massive macrophage-dominated infiltration of the mucosa and submucosa.

VIRAL CAUSES OF DIARRHEA

Feline viral enteritis usually is diagnosed in younger unvaccinated animals. The animal's signalment, history, clinical signs, and hematological findings are important in ranking a viral etiology as a likely cause of the animal's diarrhea.

Feline Panleukopenia

Feline panleukopenia (FP) is a viral disease characterized by fever, depression, anorexia, vomiting, and diarrhea. Historically, feline panleukopenia was caused exclusively by feline panleukopenia virus (FPV); however, it has now been confirmed that FP can be caused by canine parvoviruses CPV-2a and CPV-2b.[52] Feline panleukopenia has become an uncommon disease because of routine vaccination; however, outbreaks are seen occasionally in unvaccinated animals, particularly feral populations and catteries. The clinical signs are similar to those described for dogs with parvoviral enteritis.

Diagnosis

Diagnosis is based on the history, physical examination findings, results of a hemogram (neutropenia), and fecal ELISA. The ELISA test used to detect canine parvovirus has been reported to cross-react with feline parvovirus.

Treatment

Treatment is supportive and virtually identical to that described for dogs with parvovirus enteritis. Intravenous (IV) fluid and electrolyte therapy is indicated, with particular attention given to potassium repletion. The intramedullary route can be used in kittens, because the subcutaneous route is likely to be inadequate. Dextrose solution (2.5% to 5%) is added to the IV fluids if the kitten is hypoglycemic. Plasma or colloids (dextran 70 or hetastarch) are indicated if the serum albumin concentration drops below 2.0 g/dl. Antibiotics are administered to febrile or severely neutropenic cats. If the animal is neutropenic but afebrile, prophylactic administration of a first-generation cephalosporin is reasonable. Cats in septic shock should be treated with a broad-spectrum aerobic and anaerobic antibiotic (e.g., ampicillin plus amikacin). Human granulocyte colony-stimulating factor (G-CSF) at 5 µg/kg q24h SC will increase neutrophil numbers but may not influence outcome. Antiemetics such as prochlorperazine, metoclopramide, or ondansetron are indicated if vomiting is intractable. Metoclopramide is most effective when administered as a constant rate infusion at a dose of 1 mg/kg q24h. Gastric protectants including H_2-receptor antagonists and sucralfate are indicated when there is evidence of secondary esophagitis. Broad-spectrum anthelminthics to treat concurrent intestinal parasites should be administered when the cat is no longer vomiting. Most cats can be weaned gradually onto a digestible commercial enteral diet; however, intractable vomiting may warrant the administration of total or partial parenteral nutrition (see Chapter 16).

Feline Enteric Coronavirus

Feline enteric coronavirus is related to FIP-producing strains of coronavirus and invades the enterocytes at the tips of the villi. Infected cats may be asymptomatic or develop mild, transient diarrhea and fever. Infected cats can seroconvert and test positive on FIP serological testing. In addition, feline enteric coronavirus may mutate to FIP virus.

EMPIRICAL THERAPY FOR KITTENS WITH DIARRHEA OF UNKNOWN CAUSE

Unlike acute diarrhea, which often is self-limiting and may be managed with symptomatic or supportive therapy, chronic diarrhea usually requires specific diagnosis and therapy. Finding intestinal parasites in the feces of a kitten with diarrhea does not establish parasitism as the cause of the intestinal disease, although many kittens show a partial or complete resolution of clinical signs after administration of a broad-spectrum anthelminthic. We deworm diarrheic kittens routinely even in the face of a negative fecal flotation or negative *Giardia* ELISA. Serological screening for feline leukemia virus is

recommended for kittens with chronic diarrhea that have not responded to antiparasitic and dietary therapy. Metronidazole administration often is associated with some amelioration of diarrhea, possibly because of altering the intestinal microflora, dampening cell-mediated immunity, or killing a specific pathogen such as *Clostridium difficile*. Dietary modification should be considered in cats that fail to respond to empirical antiparasitic therapy and metronidazole administration. We frequently use commercial feline intestinal diets and have had success using a diet that is highly digestible and contains relatively large amounts of fermentable fiber. Kittens that fail to improve on a commercial diet can be fed a cooked turkey or chicken diet (without carbohydrates) for 5 to 10 days to provide a highly digestible meal containing moderate amounts of fat. Dietary fat restriction does not appear to be as important in cats with intestinal disease as it is in dogs. Home-cooked diets are not complete and balanced and should not be fed to kittens for more than 10 days.

Inflammatory bowel disease primarily is a disease of middle-aged to older cats, and kittens are more likely to have diarrhea resulting from an infectious cause. We discourage the administration of prednisone to diarrheic kittens unless a comprehensive work-up, including intestinal biopsies, warrants this therapy. Kittens with chronic ileitis could have secondary deficiencies of vitamin B_{12} (cobalamin), an important micronutrient for DNA replication in the intestinal crypts (see Chapter 13). Vitamin B_{12} can be administered empirically to kittens at 100 µg per kitten, given subcutaneously once weekly for 4 to 6 weeks. Repeat injections should be based on determination of serum cobalamin concentrations. Cobalamin is safe, easy to administer, and cheap. Use of prebiotics and probiotics for diarrheic animals has received tremendous attention recently; however, most studies completed have not been performed in animals with clinical disease. Furthermore, caution should be heeded when purchasing over-the-counter commercial probiotics because little federal regulation and quality control exist over many products, and label descriptions do not always match the ingredients.

CONCLUSION

Comprehensive fecal exams are pivotal in the diagnostic evaluation of kittens with diarrhea. The diagnostic yield will be increased markedly with the examination of fresh fecal specimens, the use of a centrifugation technique with zinc sulfate solution, and the timely incorporation of immunoassays for diagnosing *Giardia* and *Cryptosporidium* spp. Diagnosis of *T. foetus* is enhanced greatly with the utilization of InPouch culture kits that facilitate the growth and direct visualization of motile trophozoites. The clinical documentation of enteropathogenic bacteria that cause diarrhea in cats is clouded by the presence of many of these organisms existing as normal constituents of the indigenous intestinal flora. Attributing disease to a putative bacterial enteropathogen(s) in kittens should be made only after considering the animals' signalment, predisposing factors, clinical signs, serological assays for toxins, fecal culture, and/or PCR. Relying on results of fecal culture alone is wrong, because *C. perfringens*, *C. difficile*, *Campylobacter* spp., and pathogenic and nonpathogenic *E. coli* are isolated commonly from apparently healthy cats. Fecal cultures may be useful in procuring isolates for the application of molecular techniques such as PCR for detection of specific toxin genes, or for molecular typing of isolated strains to establish clonality in suspected outbreaks. Accurate diagnosis of infections may require diagnostic laboratories to incorporate PCR-based assays using genus- and species-specific primers to facilitate detection of toxin genes and differentiation of species that appear similar phenotypically and biochemically.

In assessment of a diarrheic kitten not responding to therapy and for which a diagnosis has not been made, repeating previously negative diagnostic tests frequently is more helpful than performing endoscopy and biopsy. The intestinal tract is a lymphoid organ (in addition to its absorptive and endocrine functions) and is expected to respond to antigenic stimulation with some degree of lymphoid hyperplasia. Simply finding intestinal lymphocytic or plasmacytic infiltrates does not mean that the kitten has inflammatory bowel disease, nor does it guarantee that steroid therapy will not be harmful.

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Chapter 16

Nutrition for Anorectic, Critically Ill, or Injured Cats

Debra L. Zoran

Nutrition is a vital aspect of the medical management of many, if not all, feline patients with critical illness or severe trauma. However, any cat with an illness that results in significant weight loss, inability to eat, or special dietary needs may require nutritional support. Successful implementation of nutritional support determines whether a positive outcome ensues. Because of the unique nutritional needs of cats, the role of nutritional support in the management of illness or trauma becomes even more essential.

One of the more important issues confronting clinicians treating cats with chronic illnesses such as chronic progressive renal disease, hyperthyroidism, or diabetes mellitus is maintenance of body weight and quality of life. Loss of muscle mass resulting from poor intake, low-protein diets, or the accompanying chronic metabolic disturbances is a frequent complication of these illnesses in old cats. This muscle wasting leads to a poor quality of life. Many cats benefit from aggressive medical therapy of their condition and from appropriate nutritional support (including placement of feeding tubes) to allow better overall management of their condition. This chapter reviews the development and implementation of an appropriate feeding plan, using either enteral or parenteral nutrition techniques, for cats that are anorectic or unable to eat as a result of injury or illness. In addition, the selection of the best diet, feeding frequency, and amount of food for the problem at hand are reviewed.

STRESSED VERSUS NONSTRESSED (SIMPLE) STARVATION

Two important types of starvation confront our feline patients in practice: (1) simple starvation and (2) stressed starvation. When a healthy animal does not consume adequate calories, this is called simple starvation, and the body's response is to increase the breakdown of fat for energy, to conserve lean muscle mass, and to down-regulate energy expenditure. This metabolic process is universal for most species. However, cats are unique in that although they can down-regulate their energy requirements and increase utilization of fat, their need for protein is unchanged and not conserved.[1]

Cats have a need for a constant source of protein and amino acids in their daily diet, because the metabolic machinery that controls their utilization of protein for energy is not able to be down-regulated during periods of low protein availability.[1,2] Therefore, in contrast to dogs, cats that are anorectic (e.g., undergoing simple starvation) for more than a day or two begin to break down muscle and other proteins, in addition to fat, to maintain their metabolic and energy needs (in addition to their protein needs for immune function, repair, and synthesis of new proteins). The consequence of simple starvation (purposefully or accidentally) in cats, especially obese cats, is well known and potentially devastating: development of hepatic lipidosis. However, this concept also is key to understanding the importance of early nutritional support in apparently healthy cats that are injured or are suddenly unable or unwilling to eat.

Stressed, or hypermetabolic, starvation is a process set into motion in critically injured or ill animals that places them at high risk for malnutrition and its deleterious effects. In contrast to simple starvation, in which both glucose and fat are used as energy sources, hypermetabolic starvation results in alterations in energy metabolism (e.g., inability to utilize glucose efficiently for energy because of the anti-insulin effects of stress hormones) and increased utilization of protein and fat.[3] The consequences of this hypermetabolic condition in the presence of lack of intake (anorexia or hyporexia) are compromised immune function (resulting in increased susceptibility to sepsis and bacterial translocation), decreased wound healing (because of protein malnutrition), and an overall negative impact on

survival.[4-6] In sick cats, the increased metabolic demand for protein and fat-based energy sources only compounds the critical need for early nutritional support. The 3- to 5-day rule is used as a reminder for determination of when nutritional support should be considered or implemented. Nutritional support *planning* should be initiated in cats that have been anorectic for 3 days, and if the cat has not started consuming adequate calories by day 5, nutritional support should be *instituted*. In short, if oral intake is inadequate, provision of nutritional support by either enteral or parenteral means is vital in a very clearly defined (3 to 5 days) period of time.

ENTERAL OR PARENTERAL NUTRITION: SELECTING A ROUTE

Oral feeding remains the ideal means of intake; however, several key factors must be considered with oral feeding in cats. First, it is essential to know how much food they should consume in a day and to monitor this amount carefully to see if that goal is being reached. Second, appetite is affected by many nonillness factors (e.g., palatability of food, environment in which the cat is fed, and food consistency, temperature, and texture) that may influence whether a cat will eat in the hospital environment.[2] These factors must be taken into account before completely abandoning oral intake in an anorectic cat. Finally, food aversion is a phenomenon occurring in cats after force feeding or when nausea or vomiting occurs after food consumption.[7,8] Food aversion is a major reason why, when they return home, many cats will not eat a therapeutic diet that has been force fed in the hospital or fed to them before nausea and vomiting was controlled completely. Once food aversion has developed, it may last months or longer.[8] In anorectic cats that have no apparent medical reason for their unwillingness to eat, appetite stimulants should be considered before more aggressive enteral or parenteral nutrition is initiated. The most commonly recommended and safest appetite stimulant for cats is the serotonin antagonist cyproheptadine (2 mg/cat PO q12h for 3 days).[5,7] Other appetite stimulants suggested for cats are the benzodiazepines, anabolic steroids, megestrol acetate, and propofol; however, each of these has potentially dangerous side effects, including liver failure, diabetes mellitus, excessive sedation, and blood dyscrasias.[7]

The feeding route selected for a particular cat is based on the premise that it is best to feed via the gastrointestinal (GI) tract if possible and to use as much of the GI tract as is functional. In other words, if the cat has esophageal disease, placement of a stomach tube often is recommended. However, if the cat has a severe case of gingivitis or stomatitis and is unable (or unwilling) to eat, an esophagostomy tube is reasonable. The second rule of thumb is to determine what feeding method is best suited for the patient's situation. Several key questions should be considered when this determination is made: (1) Is the feeding tube going to be required long term? (2) Is there an anesthetic risk that makes tube placement unacceptable? (3) What types of diet does the patient require (can the necessary food be fed through the tube selected)? (4) Is the GI tract working, and if so, is it safe to use it? Finally, the owner must be included in the decision-making process, because they must be willing and able to provide the necessary nutrition if the cat is to be able to go home. Many owners can handle the three to four daily feedings that typically are required for esophageal or stomach tubes. However, in patients with jejunostomy tubes, feeding is best implemented with use of very frequent small meals (e.g., every 2 to 3 hours) or by continuous infusion of food using a fluid pump. Therefore choosing the best feeding method requires a nutritional assessment of the individual patient's needs and an assessment of ability of the caregivers to provide the nutrition appropriately.

ENTERAL OR PARENTERAL NUTRITION: FEEDING METHOD

Many feeding methods are available for enteral nutritional support, including nasoesophageal (NE), pharyngostomy, esophageal (E), gastrostomy (G), endoscopically placed gastrostomy (PEG), and jejunostomy (J) tubes. Each of these enteral nutrition routes has advantages and disadvantages, which are presented for comparison in Table 16-1.[9] Further discussion of these individual feeding methods is found later in this chapter.

In addition to enteral nutrition, two major types of parenteral nutrition exist: total parenteral nutrition (TPN) and partial parenteral nutrition (PPN) (Table 16-2).[10,11] TPN and PPN are useful forms of nutritional support for cats and enable the clinician to provide protein and calories for patients that are unable to tolerate enteral nutrition (e.g., pancreatitis, protracted vomiting, severe intestinal disease, central nervous system disease), or in comatose cats for which enteral nutrition is dangerous (because they are unable to protect their airway). Although intravenous nutrition provides protein and energy for cats unable to eat, these forms of nutritional support do not support gastrointestinal health. The GI tract receives its nutrition directly from luminal nutrients (glutamine in particular), so whenever possible, early introduction of enteral nutrition is important, even if it is in the form of microenteral nutrition (e.g., small amounts of enteral nutrition intended to provide nutrition to the gut but not designed to support caloric needs).[12] Although the exact amount of nutrition required to support normal gut function in cats is unknown, as little as 10 ml/kg of liquid nutrition is sufficient to maintain enterocyte health in human beings.[13] TPN is used to provide 100 per cent of the patient's energy requirements intravenously, whereas PPN provides only 40 to 70 per cent of the patient's energy requirements and usually is used in combination with enteral or microenteral nutrition.[11,14]

The other difference between PPN and TPN solutions is their respective osmolarities. Most TPN solutions have an osmolarity of greater than 1000 mosm, primarily because of the 50 per cent dextrose used as the carbohydrate source. Therefore TPN must be administered via a large-bore central (e.g., jugular) intravenous catheter to avoid thrombophlebitis and venous thrombosis. PPN solutions have a lower osmolarity (usually less than 750 mosm), resulting from dilution of their contents by using 5 per cent dextrose as the carbohydrate source.[11,14] PPN may be administered via a dedicated peripheral vein with use of either a short or long indwelling catheter. However, because PPN solutions provide only 50 per cent of a patient's daily caloric needs, they can be used only as a short-term (less than 5 days) means of nutritional support (unless they are combined with enteral nutrition, which provides the other 50 per cent of the caloric needs).

Several problems arise for veterinarians wishing to use parenteral nutrition, and these are related primarily to formulation of the solution, maintenance of a sterile catheter site and

Table 16-1 | **Enteral Nutrition Routes**

ROUTE	ADVANTAGES	DISADVANTAGES	OTHER
Oral or force feeding	No special equipment Physiological method of feeding if tolerated by patient	Anorectic or painful animals will refuse or fight feeding Stressful to both the animal/caregiver Difficult to achieve caloric requirements	May induce food aversion
Nasoesophageal (NE) tube	Placed rapidly No need for anesthesia, only local anesthetic (proparacaine) No special equipment needed for placement Excellent for short-term feeding (2-3 days) in cats	Patient discomfort May be easily dislodged by patient Must use liquid diets only, thus special diets more difficult to administer Contraindicated in comatose, recumbent, or dysphoric cats that are at risk for aspiration	Caution advised in placing an NE tube in any patient with nasal disease, a clotting disorder, or severe thrombocytopenia
Esophagostomy (E) tube	Placed rapidly (5-10 minutes) Requires only short-term or light anesthesia Can use commercial feeding tubes and kit or "homemade" materials (e.g., red rubber catheter) Can use blenderized canned or liquid foods Well tolerated for long periods (weeks to months)	Vomiting may result in tube being expelled or retroflexed into the nasopharynx Tube site requires daily care to prevent infection Cannot be used in comatose, recumbent, or dysphoric animals at risk for aspiration Should not be used in animals with esophagitis or severe esophageal dysfunction Most common complication is infection at tube site	Tube can be removed at any time after placement, as permanent stoma does not form and site heals rapidly Tube does not interfere with eating; many cats will start eating with the tube in place, which may not occur with NE or pharyngostomy tubes
Gastrostomy or PEG tube	Can use commercial feeding tubes and kit or "homemade" materials (e.g., Pezzer catheter) Can use blenderized canned or liquid foods Well tolerated for long periods (weeks to months) and is best method for prolonged (months to years) feeding Can be placed with use of endoscope, an ELD device, or at surgery Excellent for cats with oral or esophageal disease	Requires longer anesthesia period for placement Requires some special equipment and expertise Complications from tube placement are more serious (e.g., peritonitis, tube leakage into abdomen)	Well tolerated by most animals for long periods Easy to access tube for feeding
Jejunostomy (J) tube	Excellent means of providing enteral nutrition for hospitalized patients with severe vomiting, gastric disease, or pancreatitis	Placement requires special equipment, endoscopic expertise, and/or surgical skill Must feed liquid diets Best to feed with continuous infusion (pump) to avoid overload of intestines with boluses of food	An important means of delivering nutrition in special situations

Table 16-2 | **Comparison of Total Parenteral Nutrition (TPN) and Partial Parenteral Nutrition (PPN) as Nutritional Support Methods**

	TPN	PPN
Catheter placement site	Central (jugular) required, must be surgically (sterile) placed	Peripheral or central, dedicated only to PPN
Osmolarity of solution	1200 mosm	600-750 mosm
Catheter type	Dual lumen or Silastic	Standard
Nutrition provided	100 per cent RER	40 per cent to 70 per cent RER
Complications	Hyperlipidemia Hyperglycemia Hyperammonemia Electrolyte disturbances Thrombophlebitis Sepsis Volume overload	Thrombophlebitis Sepsis Volume overload
Monitoring	TPR, blood glucose, serum triglycerides, and electrolytes every 4 to 6 hours or a minimum of twice daily once stable on the solution In very ill animals, CBC and chemistry profile daily	TPR, blood glucose, and electrolytes once or twice daily

Table 16-3 | **Examples of Preprepared Commercially Available PPN Solutions**

SOLUTION (COMPANY)	PROTEIN SOURCE	CARBOHYDRATE SOURCE	OSMOLARITY
Procalamine (McGraw)	3 per cent amino acids	3 per cent glycerol	735 mosm/L
Travasol 2.75 per cent in D5W (Clintec)	2.75 per cent amino acids	5 per cent dextrose	530 mosm/L
Travasol 4.25 per cent in D5W (Clintec)	4.25 per cent amino acids	5 per cent dextrose	680 mosm/L
Aminosyn II 3.5 per cent in D5W (Abbott)	3.5 per cent amino acids	5 per cent dextrose	585 mosm/L

set-up, and monitoring and adjustment of the nutritional plan depending on the response of the patient.[10,11] Many cats on TPN require significant adjustments in the formulation after initiation of feeding. The problems encountered include hyperglycemia, which requires either insulin therapy or reduction in the percent of calories provided by dextrose; hyperlipidemia, which requires a reduction in the per cent of lipid in the solution; or hyperammonemia, which requires a reduction in the amino acid portion.[5,11] In addition to these considerations, patients that receive TPN must be monitored carefully for development of fever suggesting bacteremia or sepsis, and thromboembolism, because these are important complications of this form of nutritional therapy.[5]

One major advantage of PPN over TPN is that hyperglycemia, hyperlipidemia, and hyperammonemia are less common complications; therefore the intensity and frequency of monitoring required for cats receiving this form of nutritional support are more feasible in the private practice setting. In addition, PPN solutions can be purchased premixed (Table 16-3), which precludes the need for a sterile mixing area, proper calculation of nutrient mixtures, and preparation of the solutions. In short, although PPN cannot be used for long-term nutritional support, it is a convenient and viable means of providing "bridge" nutrition until other forms of nutritional support are instituted.

ENTERAL AND PARENTERAL NUTRITION: SETTING UP A FEEDING PLAN

Once the feeding route is selected, the next step is to set up a feeding plan. Several steps are involved in setting up a feeding plan, and the first is to determine how many calories are needed for that patient. Second, for enteral nutrition, the type of food to be fed must be selected (based on the type of tube placed, food availability, and the nutritional needs of the sick cat); for parenteral nutrition, the parenteral formula must be determined. Finally, the timing, frequency, and amount of food to be fed at each meal must be determined.

The caloric needs of an individual patient can be determined by a number of different equations. In general, for very sick patients that have not been eating well or that are predisposed to vomiting, the goal should be to reach the cat's resting energy requirement (RER) for calories.[6,10,14] In the past, many nutritionists recommended calculating an illness energy requirement (multiplying the RER by a factor of 1.5 or more) to meet the higher energy needs of metabolic stress. However, recent evidence suggests that in illness, the RER reflects the true nutritional needs of sick patients more accurately, and excess calories may result in greater GI upset, bloating, or diarrhea.[14] The equation for calculation of RER used by most nutrition experts is the exponential equation[5,6,10,11]: $RER = 70(BW_{kg})^{0.75}$. However, an easier equation to use in the clinical situation is the linear equation: $RER = 30(BW_{kg}) + 70$. This equation works well for calculating RER for cats because it is more accurate (closest to the exponential equation) in small animals. In kittens or cats that weigh less than 2 kg, the exponential equation should be used for accuracy. A worksheet for developing a feeding plan for providing enteral nutrition is presented in Table 16-4.

Table 16-4 | **Feeding Plan for Enteral Nutrition**

Step 1. Calculate resting energy requirement (RER): _____

$RER = 70 (Body\ weight_{kg})^{0.75}$ or:
$RER = 30 (Body\ weight_{kg}) + 70$

Step 2. Determine food to be used and the kcal/ml of the food: ____
- Clinicare (Abbott labs): 1 kcal/ml, 300 ml/can
- Hill's a/d: 1.3 kcal/ml undiluted, 1.0 kcal/ml diluted with 50 ml water
- Eukanuba Maximum Calorie: 2.1 kcal/ml undiluted, 1.6 kcal/ml diluted with 50 ml water
- Hill's i/d: 0.9 kcal/ml undiluted, 0.6 kcal/ml diluted with 100 ml water and blended

Step 3. Set up a feeding schedule:
- Day 1: ½ RER = _____ divided into 3-6 meals/24 hr = _____ml food/meal
- Day 2: ¾ RER = _____ divided into 3-6 meals/24 hr = _____ ml food/meal
- Day 3: RER = _____ divided into 3-6 meals/24 hr = _____ ml food/meal
- Day 4: Take RER and divide into 3-4 meals/day = _____ ml food/meal

Once the RER is calculated, the next step is to select the diet that meets the needs of the cat's medical condition (e.g., highly digestible or high-energy/recovery diet, hypoallergenic or hydrolyzed diet, renal diet). This is a subject of considerable importance but is beyond the scope of this chapter. The reader is referred to several recent reviews covering this subject for an in-depth treatise of appropriate diet selection for enteral nutrition of specific diseases.[5,15] However, a few key points critical to the proper selection of diets for the type of feeding tube to be placed must be considered. For tubes of a smaller diameter, especially NE or J tubes (which usually are 5-French or smaller) a liquid diet is required, because even well blenderized and strained canned foods will plug the tube. The most widely available liquid diet for dogs and cats is a balanced but high-energy (moderate fat, high carbohydrate) diet (Clinicare, Abbott Labs, North Chicago, Illinois). This is a very good "illness" diet for dogs or cats with normal GI function; however, in patients with significant GI disease, or those that are fat intolerant or that require a low-carbohydrate diet, this food may not be an appropriate choice.

A wide range of products are available for human enteral nutrition with varying fat, protein, and carbohydrate

Table 16-5 | **Feline Liquid Diet Recipes Using Human Enteral Diets**

HIGH-ENERGY DIET

1 can Sustacal (8 oz)
1 can Pulmocare liquid (8 oz)
2 cc Lixotinic (or other B vitamin supplement)
5 Tbsp casein powder (Casek, calcium caseinate powder)
½ tsp taurine

Blend all together, keep in refrigerator (up to 1 week), Calories: 1 kcal/ml.

LOW-FAT ENTERAL DIET

1 packet	Vivonex TEN
250 ml	8.5 per cent Aminosyn (amino acid solution)
3-5 ml	Lixotinic
350 ml	Deionized water

Mix together and store in refrigerator (up to 48 hr), Calories: 0.6 kcal/ml

Table 16-6 | **Peripheral Parenteral Nutrition (PPN) Worksheet**

1. Calculate resting energy requirement (RER):

$$RER = 70(BW_{kg})^{0.75} = \_\_\_\_\_$$

or

$$RER = 30(BW_{kg}) + 70 = \_\_\_\_\_$$

2. PER = partial energy requirement = RER × 0.50 = _____
3. Nutrient requirements:

Standard formulation = 33 per cent protein, 33 per cent lipid, 33 per cent carbohydrate
Formulation for most cats:

PER × 0.25 = _____ kcal/day from dextrose (5 per cent)
PER × 0.25 = _____ kcal/day from amino acids (8.5 per cent)
PER × 0.50 = _____ kcal/day from lipid (20 per cent)

4. Volume of nutrient solutions:

5% dextrose = _____ kcal/day ÷ 0.17 kcal/ml = _____ ml/day
8.5% amino acids = _____ kcal/day ÷ 0.34 kcal/ml = _____ ml/day
20% lipid = _____ kcal/day ÷ 2.0 kcal/ml = _____ ml/day

5. Total daily requirements:

_____ ml 5 per cent dextrose
_____ ml 8.5 per cent amino acids
_____ ml 20 per cent lipid
_____ ml total volume PPN solution/24 hr

Total ml divided by 24 = ml/hr infusion rate*

* This calculation should approximate a cat's maintenance fluid requirements, so it is important to adjust the IV fluids accordingly. In cats with cardiac or renal disease, this rate may exceed their ability to handle the fluid volume, so the rate of PPN may have to be reduced.
Vitamins may be added to the PPN solution (3 to 5 ml/day multi-B complex) or to the IV fluids as desired.

concentrations, and these can be used for short-term feeding. However, because human enteral diets do not provide adequate protein (most have 15 to 18 per cent protein) and are deficient in a number of amino acids (e.g., taurine, arginine, and carnitine) and other nutrients (e.g., arachidonic acid, certain B vitamins) that cats require, they should not be fed for more than 2 to 3 days without supplementation of these nutrients. Table 16-5 provides a recipe for modification of human enteral formulations to provide more appropriate nutrition for cats. Most E or PEG tubes are 10-French or larger and accommodate most canned foods that are blenderized into a gruel or slurry. Remember that when water is added to the food for blenderization, the calories are diluted. For example, diluting a can of Hill's Prescription diet a/d with 50 ml water will alter the caloric density from 1 kcal/ml to 0.8 kcal/ml. This effect can be decreased by using Clinicare instead of water to dilute and liquefy the canned food.

If parenteral nutrition is the route of nutritional support selected, the first major decision in nutrition planning is to determine whether TPN or PPN is to be used, because the type of catheter used and its placement are crucial. The next step is to determine the formulation that best fits the cat's nutritional needs (Table 16-6). For cats with renal insufficiency, liver failure, diabetes, or other significant metabolic disturbances, TPN formulation is complicated and should be done in consultation with a nutritionist. In general, when using PPN for nutritional support, the calories are divided evenly between the nutrient groups (33 per cent protein, 33 per cent lipid, 33 per cent carbohydrate). Alternatively, a solution containing 50 per cent lipid, 25 per cent carbohydrate, and 25 per cent protein can be formulated to provide additional energy. If additional protein is desired, the formula can be altered to be 50 per cent protein, 25 per cent carbohydrate, and 25 per cent lipid.[11,14] If a PPN solution is compounded by the attending clinician, a laminar flow hood should be used in combination with strict aseptic technique, using a closed-system, parenteral nutrition compounder to ensure the sterility of the solution.

Once a solution is prepared, it must be used or discarded within 48 hours, and ideally the solution should be divided so that 50 per cent of the volume is stored in the refrigerator while the first half is used. Because of the difficulties and cost effectiveness, many practices choose to have their TPN or PPN solutions compounded by a local human hospital or human home health care company. When compounding is not feasible, commercial ready-to-use PPN solutions may be used. These preparations generally are composed of glucose (or glycerol) and 2.5 to 3.5 per cent amino acids (see Table 16-3) and provide only 30 to 40 per cent of the caloric needs when administered at maintenance fluid rates; therefore this may not be suitable for all settings. Further, in cats, the amount of amino acids provided with the premixed solutions is inadequate to prevent protein malnutrition if they are administered for several days. However, for short-term, "bridge" nutritional support, these solutions provide some amino acids and energy in the form of carbohydrate that may be life saving until more appropriate nutritional support can be provided.

Once the amount and type of food are determined, a plan is developed to deliver the nutrients efficiently while minimizing vomiting or other complications. In most cats, small, frequent meals are tolerated more readily than large boluses of food because the feline stomach is not as readily distensible as that of dogs or other species.[2] Gastric volume in small animals is approximately 60 ml/kg, and a good rule of thumb to reduce the risk of vomiting in cats because of overfeeding is to avoid feeding a volume of food at any one feeding that exceeds 50 per cent of this capacity.[5] When feeding is initiated in cats, the goal on the first day is to provide four to six meals over the course of the day, with half of the RER as the caloric goal. If that amount of food is tolerated, the feedings are increased by one fourth on the second day, and so on. Some cats with GI disease are not able to tolerate the volume of food required to

meet RER; however, even a small amount of food provides nutrients to the GI epithelial cells, which preserves intestinal mucosal health and minimizes the risk of intestinal bacterial translocation. In cats that are unable to tolerate all of their caloric needs enterally, a combination of enteral and parenteral nutrition may offer the best means of providing this nutritional support.

MONITORING OF NUTRITIONAL SUPPORT

Enteral nutrition is preferred over intravenous nutritional support, because it is easier to administer and more physiological (e.g., nutrition received via the GI tract is processed more efficiently, safely, and physiologically) for the cat and because it is safer and generally associated with fewer side effects.[6,7,9] However, the most common problems are associated with tube issues (see later), or vomiting or diarrhea resulting from overfeeding or GI dysfunction. The key is to start slowly and increase the amount of nutrition provided only when it is apparent that the patient is tolerating the feedings well. Enteral nutrition also is less likely to be associated with refeeding syndrome (hypophosphatemia, hypomagnesemia, and other electrolyte disturbances that occur as a result of feeding after a long fasting/anorectic period) than parenteral nutrition, so frequent measurement of electrolytes and other laboratory parameters is less essential. Numerous potential complications of TPN or PPN occur, including metabolic disturbances (e.g., hyperglycemia, electrolyte abnormalities, hypertriglyceridemia), mechanical problems of the catheter or lines, and septic complications.[5,10,14,16] Because of these potential problems, careful monitoring is essential and must be tailored to the individual patient's medical condition and circumstance.

The following parameters should be measured daily (if not multiple times daily) in all cats that receive parenteral nutrition: temperature, pulse, respiration, attitude, body weight, catheter site observation, blood glucose, hematocrit and total serum protein (examine serum for gross lipemia), and electrolytes. In some cats, a complete blood count and a chemistry profile may be indicated, especially those with organ dysfunction or septicemia. The key point is that intravenous nutrition requires more careful and frequent monitoring of the cat's systemic response than enteral nutrition, and this must be factored into the nutritional support plan presented to the owner.

PLACEMENT OF FEEDING TUBES FOR ENTERAL NUTRITION

Once the feeding plan has been developed, it is time to place the tube and begin nutritional support. The reader again is referred to several recent reviews for specific information about tube placement.[8,15,17] However, a few comments about the different types of tubes, their use in specific situations, and the potential complications associated with their use are presented.

NE Tubes

NE tubes are an important feeding option for all hospitalized cats that require short-term feeding but that are unable or unwilling to eat.[5,17,18] These tubes are placed easily in most cats after instillation of local analgesia (proparacaine ophthalmic drops) in the nose, or mild sedation (e.g., buprenorphine) for those animals that are extremely anxious. The main contraindications to use of NE tube feeding are severe nasal disease when passing the tube may be difficult or impossible, animals with a coagulopathy (tube placement may cause epistaxis), severe/uncontrolled vomiting (the tube will not stay in place), and in any patient that is unable to protect its airway (comatose, laterally recumbent animals that are at risk for aspiration). This type of feeding is best used short term, because most cats will not tolerate the tube in their nose for more than a few days. Because the NE tubes placed generally are 3.5-French or 5-French in size, only liquid diets can be fed. Cats with NE tubes can be fed intermittently with small, frequent (four to six daily) meals administered by syringe or continuously by attaching the tube to an infusion pump for slow, constant feeding. Avoiding feeding the cat a large bolus of food is important, because that may result in vomiting due to gastric overdistension, or diarrhea caused by rapid gastric emptying of the liquid diet into the small intestine (a condition similar to "dumping syndrome" in human beings).

Pharyngostomy and E Tubes

Pharyngostomy and E tubes offer several advantages to practitioners over PEG tubes, G tubes placed with an ELD device, or surgically placed G tubes, because they can be placed without having specialized equipment or expertise. In addition, although pharyngostomy and E tubes require anesthesia for proper placement, the amount of time required is much shorter than for other procedures. For that reason, and many others, these tubes are a useful method of providing short-term or long-term enteral nutrition for cats. That being said, pharyngostomy tubes have fallen from favor compared with E tubes, because they are associated with more complications (because of their location, they interfere with epiglottic movement and laryngeal function and have been associated with recurrent laryngeal nerve injury and dysfunction) and are less well tolerated than E tubes, especially for long-term feeding.[9] Many animals are reluctant to resume eating food orally as long as the pharyngostomy tube is in place, which is not a problem in cats with E tubes.

E tubes may remain in place for months, as long as the tube site is kept clean and free of infection and is wrapped to prevent it from being removed inadvertently by the cat.[19,20] For these reasons, placement of an E tube is preferred, being the type of tube recommended most frequently for anorectic cats, cats with hepatic lipidosis, and even for cats with chronic progressive renal disease that require assistance with fluid intake and administration of medications[20] (Figure 16-1). The only major complication reported in association with E tube placement is infection at the ostomy site.[5,20] The ostomy site will not seal around the tube, so oozing around the site is common. The key to prevention of ostomy site infection is daily cleaning of the site, and if needed, because of oozing, topical application of an antibiotic cream such as silver sulfadiazine. However, the ostomy site will close rapidly once the tube is removed (inadvertently or purposely), so if a tube must be replaced, it should be done as soon as possible after it is removed (within 4 to 8 hours). The ostomy site will heal rapidly by granulation, and despite the potential for esophageal stricture or fistula formation, this complication has been encountered rarely.[5]

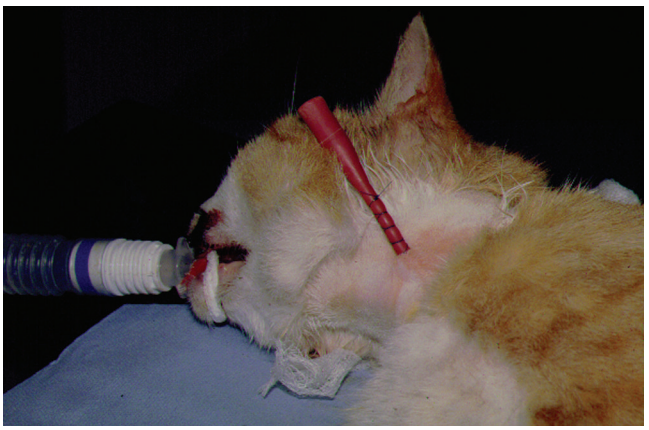


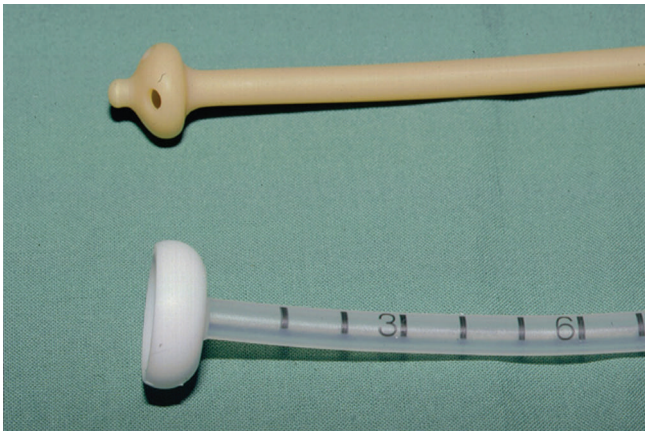
Figure 16-1. Esophagostomy tube in place on the left side of the neck in a cat, illustrating the appearance of a clean, healthy stoma site.

G Tubes: PEG and Blind Percutaneous Gastrostomy Techniques

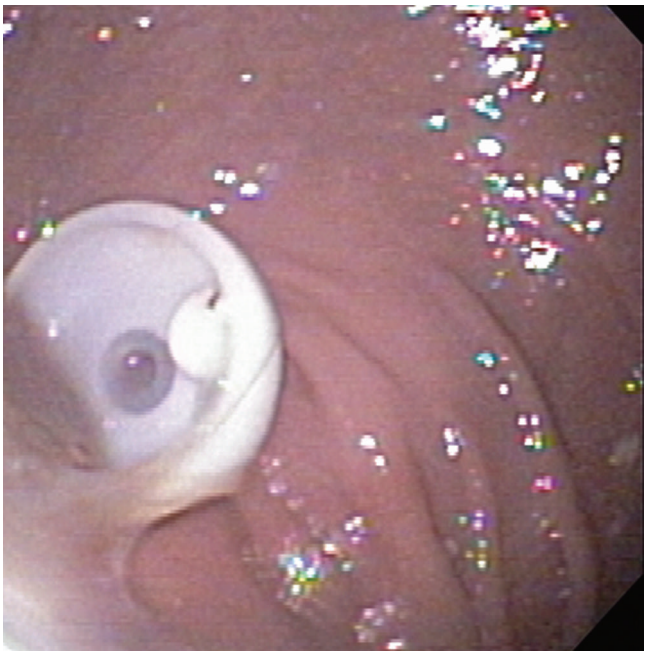
G tubes are the best method for feeding patients with severe esophageal disease, patients that are vomiting (because E tubes may be vomited up), or in cats for which long-term feeding is anticipated. The major drawbacks of using G tubes are that their placement is more complicated and requires specialized equipment (e.g., endoscopy or an ELD device), placement requires more anesthesia time, and, if they are not placed surgically and the animal is vomiting, the tube site can leak gastric contents into the abdomen. The contraindications to G tube feeding are similar to those for E tubes: they should be avoided in comatose animals (e.g., inability to protect their airway) or any patient with a gastric outflow obstruction. If these guidelines are taken into consideration, G tubes are an efficient and effective means of delivering nutrition to cats over long periods of time (months to years).

One of the many advantages of using a G tube for enteral nutrition is that diameter of the tubes placed is relatively large (e.g., 12 to 18 French) (Figure 16-2). The size of these tubes allows easy use of blenderized canned foods instead of feeding exclusively liquid enteral diets. The tubes also allow easy administration of medications, which can be difficult if not impossible or dangerous in anorectic cats. The most common tube used for G tubes in our hospital, in both cats and dogs, is the mushroom-tipped urological catheter (also called a Pezzer catheter, Bard Urologic Division, Covington, GA) (Figure 16-3). However, G tube kits (intended for human use but that work well in dogs and cats) are available (Figure 16-4) and provide a tube with all of the supplies needed to place it (except the endoscope).

Several options are available for tube placement, but the key is to become familiar with one or two so that the procedure becomes second nature.[21,22] Once a G tube is placed, it should remain in place for at least 10 to 14 days before it is removed so that the gastric stoma will form a seal that prevents leakage and form an attachment between the stomach and the body wall. If a G tube is removed accidentally before intended, a tube can be replaced through the same stoma site if the procedure is performed rapidly (e.g., within 24 hours of the tube removal). Commercial kits are available (Bard) that allow replacement of the tube through the stoma.



A



B

Figure 16-2. A, Illustration of a typical G tube available commercially. **B,** Endoscopic view of the PEG tube in place in the stomach wall.

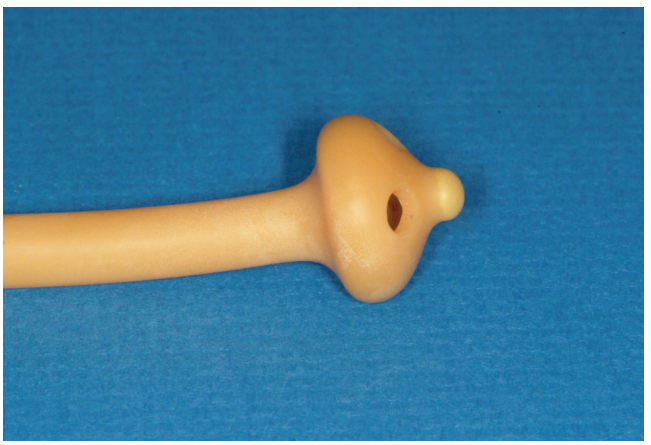


Figure 16-3. Illustration of a Pezzer urological catheter that may be used as an alternate choice for a PEG tube.

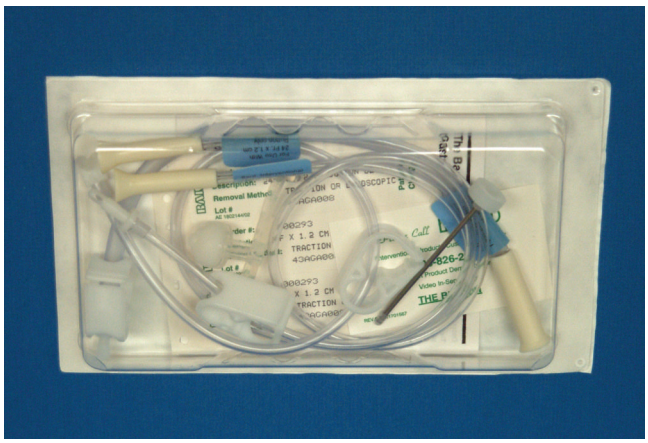


Figure 16-4. A commercially available kit for placement of a PEG tube.

An alternative procedure for placement of G tubes in dogs and cats was developed with use of a rigid device (an ELD device) that facilitates G tube placement without the need for an endoscope or surgical procedure.[21] This procedure certainly is useful in practice settings in which an endoscope is unavailable; however, some important drawbacks exist, not the least of which is that the procedure is performed blind. Therefore it is impossible to be sure of the location in the stomach where the tube is being placed. In addition, without careful diligence, perforation of the spleen, liver, or intestinal loops during the stab procedure is easy. Improperly placed tubes may result in leakage of gastric contents into the abdomen, abnormal gastric function, abnormal reflux of gastric contents into the esophagus, or vomiting resulting from gastric outflow abnormalities. The procedure has been well described elsewhere, and the interested reader is referred to these works for more information.[5,21,23]

J Tubes

Some situations arise in which enteral feeding is best accomplished if the food is delivered directly into the small intestine (e.g., some cases of pancreatitis, gastric outflow disruption, or patients with other duodenal or upper intestinal outflow issues). Until recently, placement of jejunostomy tubes was a surgical procedure performed during an exploratory laparotomy; however, several recent publications describe the placement of J tubes via endoscopic procedures.[21,24] This method may be preferred in cats for which surgical placement of the J tube is considered dangerous or the procedure deemed too stressful. The method requires placement of a J tube through an existing PEG tube and also is known as a PEG-J. This procedure is relatively straightforward but not necessarily easy to accomplish. The interested reader is referred to the above references for specific details about placement of the PEG-J tube.

An alternative method for J tube placement that is used frequently in human patients is the nasojejunostomy (nasoJ) tube. Placement of this type of J tube is described in cats and dogs, but it is more challenging technically to place. As with NE tubes, they are not as well tolerated as are J tubes placed through the G tube.[21] For that reason, the use of the PEG-J or traditional (surgical) placement of the J tube is recommended.

COMPLICATIONS OF FEEDING TUBES

Major complications of feeding tube placement in cats are uncommon and usually can be avoided with proper technique and careful client education. The most common complications are tube clogging, infection at the tube site, tube dislodgement by the animal, and vomiting after feeding. Other complications include leakage around the tube site, abnormal gastric outflow or function, diarrhea resulting from overfeeding the small intestine, necrosis of gastric wall, stricture of esophagus at the tube site, and splenic or other organ laceration/injury. Tube clogging normally can be avoided by flushing the tube carefully with water after each feeding and by using appropriate food for the size of the tube. If the tube becomes clogged, it often can be unclogged by expelling water forcefully into the tube by using a guide wire to dislodge the attached food or by instilling a small amount of carbonated cola into the tube.

In most situations, infections at or around the tube site can be prevented by careful tube site care. All tube sites should be cleaned daily, and the use of an antibiotic cream often is useful in prevention of infection, ulceration, or other tube site problems. To prevent the tube from being dislodged, careful placement of bandaging or body covers prevents inadvertent removal. If the animal is irritated by the tube, a careful assessment of the tube should be undertaken, because the tube may be getting infected or some other problem is occurring; most cats do not disturb the tube except in cases of complications. Finally, if the patient vomits after feeding, the practitioner should check to be sure that the amount (volume) of food being given is not excessive (i.e., feed smaller, more frequent meals initially) or add a prokinetic (e.g., metoclopramide, cisapride, ranitidine) or antiemetic drug (metoclopramide, dolasetron, chlorpromazine) to the regimen. In most cases, the complicating factors can be resolved and successful enteral feeding completed if alterations in volume, frequency, or type of food are made.

SUMMARY

Nutritional support is an essential part of successful treatment of many feline diseases. Although oral feeding remains the easiest method and is the ideal approach to achieving adequate intake, many ill cats cannot or will not eat enough to meet their daily protein and energy needs. Further, force-feeding and nausea can cause food aversion in cats, so this must be considered in any patient for which a particular diet is required (e.g., renal diets). If the cat develops a food aversion, it will not consume the therapeutic diet later. Tube feeding and intravenous nutritional support are options available to ensure that the feline patient is receiving adequate protein and energy intake.

Because all cats need protein and they are unable to downregulate protein utilization in times of stress or decreased intake, nutritional support should be initiated in all cats that have not eaten in 3 to 5 days. In any cat that is undergoing an anesthetic procedure after which compromised food intake is possible, a feeding tube (E, G, or J) should be placed, because removal of the tube is much easier if it is not needed than to place it at a later date. Intravenous nutritional support provides an alternative in situations in which enteral feeding is not possible or is compromised. However, because of the potential for complications, such as septicemia, coagulopathy, and

electrolyte disturbances, TPN or PPN must be used in a setting that offers appropriate monitoring and the ability to provide 24-hour assessment. Finally, with all forms of nutritional support, the response to therapy must be reevaluated continually, with adjustments made in amount, frequency, and type of food as needed. Nevertheless, in all cats, the question is not whether to feed, but when, where, and how.

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Chapter 17

Update on Hypercalcemic Disorders

Patricia A. Schenck, Dennis J. Chew, and Ellen N. Behrend

Calcium is required for many intracellular and extracellular functions in addition to skeletal support. In serum or plasma, calcium exists in three fractions: ionized, complexed (e.g., bound to phosphate, bicarbonate, sulfate, citrate, lactate, oxalate), and protein-bound.[1] In normal dogs, ionized, complexed, and protein-bound fractions account for 55 per cent, 10 per cent, and 35 per cent of serum total calcium, respectively.[2] In normal cats, these percentages are similar, with 52 per cent ionized, 8 per cent complexed, and 40 per cent protein-bound.[3] The ionized calcium fraction is the biologically active fraction.

Regulation of serum calcium is complex and involves the integrated actions of parathyroid hormone (PTH), vitamin D metabolites, and calcitonin (Figure 17-1).[1] PTH is involved in the minute-to-minute fine regulation of blood calcium concentration. When ionized calcium concentration decreases, PTH production is stimulated in the chief cells of the parathyroid glands. The most important actions of PTH are to (1) increase blood calcium concentration; (2) increase renal tubular calcium reabsorption; (3) increase bone resorption; (4) increase renal conversion of 25-hydroxyvitamin D (calcidiol) to 1,25-dihydroxyvitamin D (calcitriol, the active vitamin D metabolite); and (5) decrease renal tubular phosphorus reabsorption. Calcitriol increases both serum ionized calcium and phosphorus concentrations, primarily by increasing their intestinal absorption. Calcitriol also causes bone resorption and facilitates renal calcium and phosphorus reabsorption. Calcitonin is synthesized by the C cells in the thyroid gland in response to hypercalcemia or a calcium-rich meal. Calcitonin inhibits osteoclastic bone resorption, but its overall effects on normal calcium homeostasis are minor.

DIAGNOSTIC TESTS OF CALCIUM METABOLISM

Measurement of serum total calcium, ionized calcium, calcium metabolic hormones, and vitamin D metabolites may aid in the diagnosis of calcium disorders.

Serum Total Calcium Concentration

Measurement of total calcium concentration is part of most routine serum biochemical profile evaluations. It usually is measured by a colorimetric method and may be elevated spuriously if hyperlipemia or hemolysis is present. Normal serum total calcium concentration in cats generally ranges from 9.0 to 10.5 mg/dL (2.25 to 2.62 mmol/L) (Table 17-1). Reference ranges vary among laboratories; therefore, individual laboratories should establish specific reference ranges based on the methodology used.

Even though ionized calcium is the biologically active fraction, many clinicians rely on serum total calcium concentrations to predict ionized calcium status. This practice is not recommended. Adjustment formulas to correct total calcium concentration for the albumin or total protein concentration had been recommended in dogs, but have not been recommended in cats because of the poor correlation between albumin concentration and serum total calcium concentration.[4] In a recent study of 434 cats, diagnostic disagreement between serum ionized and total calcium concentrations was 40 per cent, indicating the poor predictive value of serum total calcium measurement.[5] Hypercalcemia and normocalcemia are underestimated, and hypocalcemia is overestimated when using serum total calcium concentration to predict ionized calcium status. Therefore ionized calcium concentrations must be measured directly to accurately assess calcium status.

Serum Ionized Calcium

Ionized calcium is the biologically active fraction of total calcium and is a better indicator of disease states than total calcium.[6,7] Some laboratories offer serum ionized calcium analysis, measured with an ion-selective electrode.[8] Ionized calcium concentration can be measured in serum or heparinized plasma; EDTA plasma cannot be used because EDTA chelates calcium, which results in a falsely decreased measurement. The

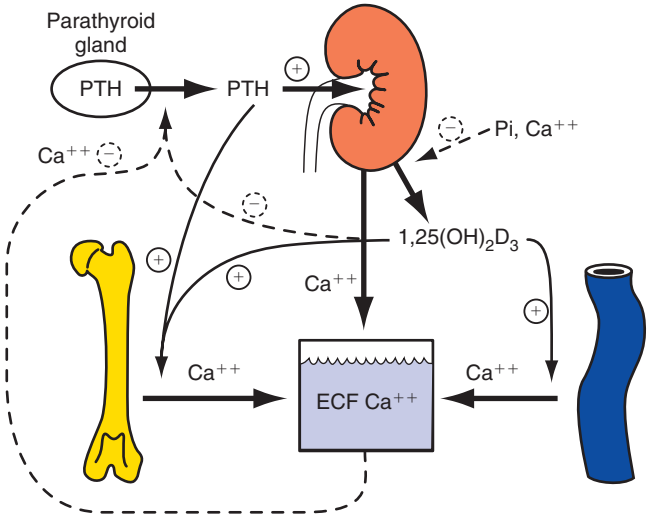

Figure 17-1. Regulation of calcium concentration by the effects of parathyroid hormone (PTH) and calcitriol ($1,25[OH]_2D_3$) on the gut, kidney, bone, and parathyroid glands. The principal actions of PTH are to increase the extracellular fluid (ECF) calcium concentrations by mobilizing calcium from bone, increasing renal tubular calcium reabsorption, and indirectly by increasing calcitriol synthesis. The main effect of calcitriol is to increase intestinal calcium absorption; however, it also exerts negative regulatory control of PTH synthesis and regulates its own synthesis. *Ca,* calcium; *Pi,* phosphorus. (Modified from Habner JF, Rosenblatt M, Pott JT: Parathyroid hormone: biochemical aspects of biosynthesis, secretion, action, and metabolism. Physiol Rev 64:1000, 1984.)

Table 17-1 | **Approximate Reference Ranges for Calcium Metabolic Hormones in Cats***

ANALYTE	REFERENCE RANGE
Total calcium	9.0-10.5 mg/dL; 2.25-2.62 mmol/L
Ionized calcium (mmol/L)	1.20-1.40
PTH (pmol/L)	0.0-4.0
PTHrP (pmol/L)	<1.0
25-hydroxyvitamin D (nmol/L)	65-170
1,25-dihydroxyvitamin D (calcitriol)	20-40 pg/mL; 50-100 pmol/L

*These values represent typical reference ranges. Reference ranges should be established for each individual laboratory based on the methodology of assay.

range for normal ionized calcium concentration generally is 4.8 to 5.6 mg/dL (1.2 to 1.4 mmol/L). Young cats (up to 2 years of age) may have serum ionized calcium concentrations that are 0.1 to 0.4 mg/dL higher than those reported in older animals.[9]

For the most accurate measurement of ionized calcium concentration, serum samples should be collected and handled anaerobically, because mixing of serum and air results in an increased pH and an artifactually decreased ionized calcium concentration.[10] Ionized calcium in anaerobic canine samples is stable after storage for 7 days at 4° C,[10] which allows sufficient time for shipment to a reference laboratory. Because anaerobic sample collection is cumbersome, some laboratories have developed species-specific pH adjustment formulas that allow measurement of ionized calcium in samples collected aerobically, with subsequent correction of the measured concentration to that present at a pH of 7.4. Although an ionized calcium concentration obtained from an aerobic sample and pH correction is not as accurate as a concentration measured in an anaerobic sample, the concentration obtained from the aerobically collected sample is still much more indicative of actual ionized calcium status than is measurement of serum total calcium concentration.

Hand-held point-of-care analyzers also are available for cage-side analysis of ionized calcium concentration. Heparinized whole blood is used for analysis; however, measured ionized calcium concentrations typically are lower (0.05 to 0.14 mmol/L) in heparinized whole blood compared with those in serum.[11] In addition, the quantity of heparin used and the volume of blood collected affect the measured ionized calcium concentration as a result of a dilutional effect of heparin. For best results, syringes preprepared with a known quantity of lyophilized heparin should be used, and the same volume of blood measured for each sample. Reference ranges should be established for each clinical setting utilizing a standard collection protocol.

Parathyroid Hormone

An intact PTH assay (a two-site assay) provides accurate determination of PTH concentration.[12,13] Serum or plasma can be assayed but should be separated from the cells and kept refrigerated or frozen before analysis to prevent PTH degradation. Ionized calcium concentration should be measured in all samples used for PTH determination. Normal serum PTH concentration in cats generally is 0 to 4 pmol/L.[14]

Parathyroid Hormone–Related Protein (PTHrP)

PTHrP is a hormone secreted by some malignant neoplasms. PTHrP can bind to PTH receptors in the kidneys and bones, causing all the same effects as PTH and resulting in humoral hypercalcemia of malignancy (HHM). PTHrP is sensitive to degradation but appears to be more stable in separated EDTA plasma (unpublished observation) as compared with serum.[15] Separated plasma should be kept frozen before PTHrP measurement. PTHrP assays have been validated for use in cats.[16]

Vitamin D Metabolites

Metabolites of vitamin D are chemically identical in all species. Serum concentrations of 25-hydroxyvitamin D (calcidiol, vitamin D_2) are a good measure of vitamin D ingestion. Normal serum concentration of 25-hydroxyvitamin D ranges generally from 65 to 170 nmol/L in cats. Serum or plasma can be assayed, but samples should be separated from the blood cells and protected from light to inhibit degradation. Calcitriol (1,25-dihydroxyvitamin D, vitamin D_3) is the active vitamin D metabolite, but unfortunately laboratory analysis is not widely available.

CLINICAL SIGNS

Clinical signs of hypercalcemia in cats vary from absent to severe but usually are insidious and often unnoticed by owners. The clinical signs differ among patients and may be referable to one or more body systems. Signs may be nonspecific (e.g., lethargy, anorexia) or referable to the urinary (e.g., polyuria/polydipsia, dehydration, hematuria/pollakiuria/dysuria), gastrointestinal (e.g., vomiting, constipation), neuromuscular (e.g., seizures, weakness), or cardiac (arrhythmias)

Table 17-2 | **Clinical Signs in 45 Cats With Hypercalcemia of Varying Etiologies**[17-27]

CLINICAL SIGN	NUMBER AFFECTED (PERCENTAGE)
Vomiting	14 (31%)
Lethargy/depression	14 (31%)
Anorexia	12 (27%)
Hematuria	7 (16%)
Dysuria	5 (11%)
Polyuria/polydipsia	4 (9%)
Stranguria	4 (9%)
No clinical signs	4 (9%)
Inappropriate urination	3 (7%)
Weight loss	3 (7%)
Pollakiuria	2 (4%)
Weakness	2 (4%)
Diarrhea	2 (4%)
Constipation	2 (4%)
Obtundation	1 (2%)
Muscle tremors	1 (2%)
Ataxia	1 (2%)
Reluctance to move	1 (2%)
Harsh vocalization	1 (2%)

systems. Table 17-2 shows clinical signs reported in 45 cats with hypercalcemia resulting from etiologies in which the clinical signs are likely to be caused by the hypercalcemia itself, that is, idiopathic hypercalcemia (n = 25),[17,18] uncomplicated hyperparathyroidism (n = 16),[19-25] and vitamin D toxicosis (n = 4).[26,27] In a small percentage of cats (9 per cent), no clinical signs were present. To some extent, the underlying cause of the hypercalcemia may affect which clinical signs are present. For example, in a study of 71 cats in which neoplasia and renal failure were the most common causes of hypercalcemia, anorexia and lethargy were reported in 70 per cent.[28]

Abnormalities noted on physical examination in the 45 hypercalcemic cats included a bilateral reduction in kidney size (n = 7, 16 per cent), tachycardia (n = 2, 4 per cent), and signs of upper respiratory tract congestion (n = 1, 2 per cent). In 19 cats with primary hyperparathyroidism, an enlarged parathyroid gland(s) was palpable in at least 11 (58 per cent).[19] Interestingly, an enlarged thyroid or thyroidal cyst was palpable in four hypercalcemic cats, two with primary hyperparathyroidism[20] and two with idiopathic hypercalcemia.[18] Therefore the presence of a palpable cervical mass in a hypercalcemic cat is suggestive of, but not pathognomonic for, hyperparathyroidism. Although the presence of palpable urinary bladder stones is rarely if ever noted, and stone formation secondary to hypercalcemia previously was considered uncommon in cats, 132 of 557 (23.7 per cent) hypercalcemic cats had uroliths detectable by radiography or ultrasonography.[17,18,21,28-30] The majority of the analyzed stones contained calcium oxalate.[18,21,28] In addition, approximately 35 per cent of cats with calcium oxalate uroliths are mildly hypercalcemic,[31] which suggests that hypercalcemia, if present, may lead to the formation of uroliths relatively frequently (see Chapter 46).

DIAGNOSTIC APPROACH

The overall incidence of hypercalcemia in cats is unknown. In dogs, the frequency of serum total hypercalcemia in more than 10,000 canine serum samples analyzed over a 6-month period at one private veterinary diagnostic laboratory serving the primary veterinary practice community was 1.5 per cent.[32] Of these, 28 per cent were from young growing dogs and therefore nonpathological; 62 per cent were transient; and 18 per cent were persistent and associated with pathology. Reports of this nature are not yet available for cats.

Table 17-3 | **Differential Diagnoses for Hypercalcemia**

Granulomatous disease
Osteolysis
Spurious (e.g., lab error; presence of lipemia, hemolysis)
Hyperparathyroidism, **H**ouse plant ingestion, **H**yperthyroidism
D toxicosis (i.e., vitamin D toxicosis), **D**ehydration
Addison's disease (hypoadrenocorticism), **A**luminum toxicity
Renal failure
Neoplasia, **N**utritional
Idiopathic
Temperature (hypothermia)

To document hypercalcemia, measurement of serum ionized calcium concentration is necessary. Hypercalcemia often is suspected based on an initial analysis of serum total calcium. The detection of a single episode of mild serum total hypercalcemia should trigger a request for a second sample to see if the results are repeatable. Mild hypercalcemia may be transient and inexplicable at times. The second sample should be collected after a 12-hour fast, because food intake can cause mild hypercalcemia. If the mild serum total hypercalcemia is repeatable, an ionized calcium concentration should be measured. If a moderate to severe elevation in serum total calcium is observed on initial sampling, ionized calcium concentration should be measured as soon as possible. Conversely, a normal serum total calcium concentration does not guarantee a normal ionized calcium concentration. In some cases, serum total calcium may be normal yet ionized calcium concentration is elevated, possibly attributable to early primary hyperparathyroidism or idiopathic hypercalcemia. Thus if a cat has a total serum calcium concentration near the upper limit of the reference range and clinical signs consistent with hypercalcemia, ionized calcium concentration should be measured.

A diagnostic approach to identifying the cause of hypercalcemia is presented in Figure 17-2. Multiple etiologies for hypercalcemia exist, and most can be remembered by the mnemonic "GOSH DARN IT" (Table 17-3). Hypercalcemia may be parathyroid-dependent (i.e., primary hyperparathyroidism) or parathyroid-independent. Primary hyperparathyroidism is caused by a PTH-secreting tumor of a parathyroid gland(s) and is characterized by elevated ionized calcium concentration without appropriate suppression of PTH production. In parathyroid-independent hypercalcemia, an elevated ionized calcium concentration suppresses PTH production, so ionized calcium concentration is elevated, and serum PTH concentration is suppressed into the lower part of the reference range. Expected concentrations of PTH and ionized calcium in cats with hypercalcemia are shown in Figure 17-3. Dogs almost always have a definable cause for hypercalcemia following routine diagnostic work-up, whereas cats often have a diagnosis of idiopathic hypercalcemia after extensive diagnostic evaluation.

The three most common differential diagnoses for persistent serum total hypercalcemia in cats are chronic renal failure, idiopathic hypercalcemia, and malignancy. Although one study states that neoplasia is the most common cause of

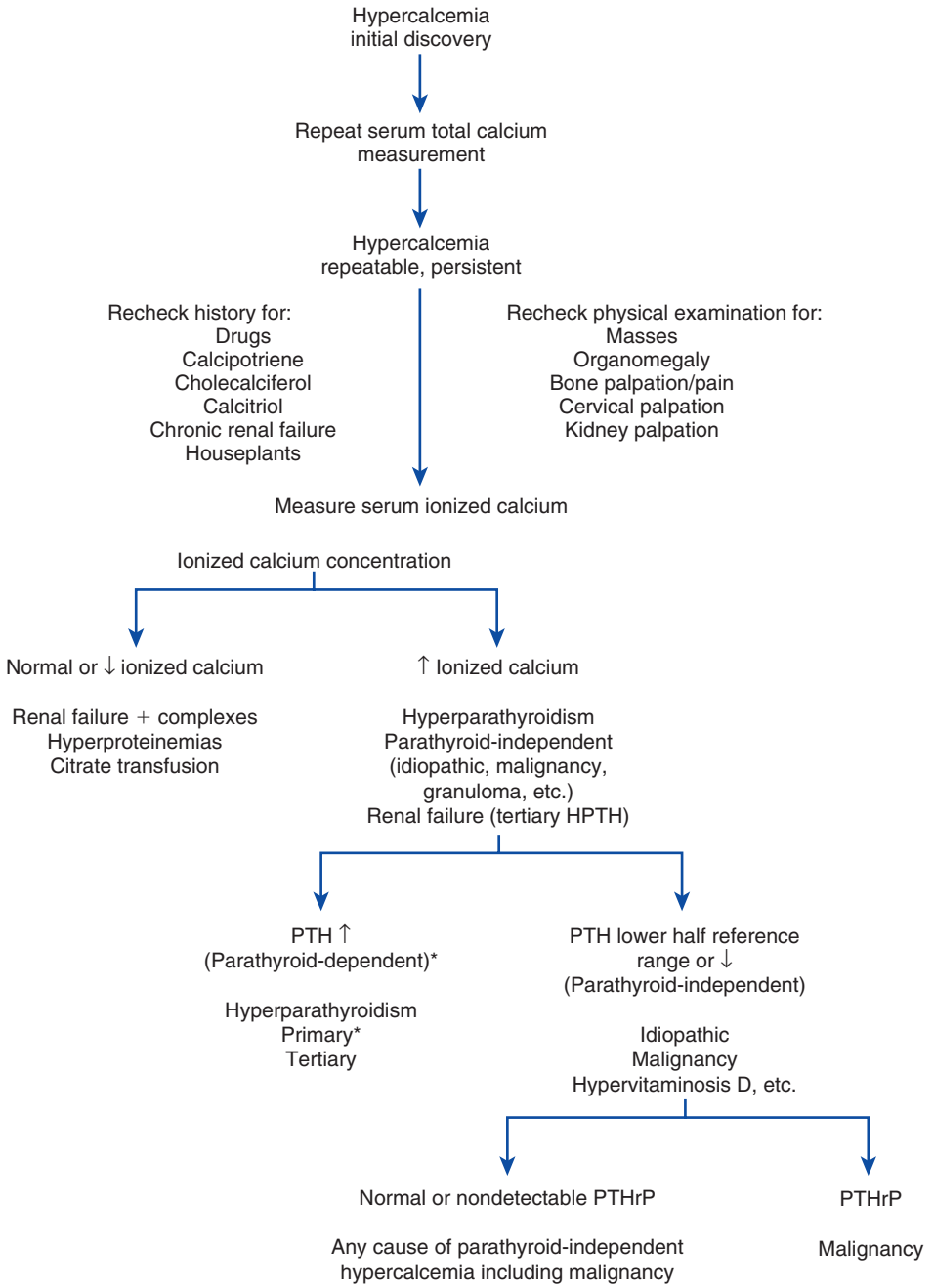

Figure 17-2. Diagnostic approach to the most common causes of hypercalcemia in cats. Some cats with primary hyperparathyroidism may have a PTH concentration in the upper end of the reference range. *HPTH,* Hyperparathyroidism; *PTH,* parathyroid hormone; *PTHrP,* parathyroid hormone related protein.

hypercalcemia in cats,[28] reevaluation of the data provided could suggest the most common cause is renal failure. The 71 cats were categorized into disease groups, and 21 were classified in the neoplasia group, 18 in the renal failure group, and 11 in the urolithiasis group. However, one interpretation could be that urolithiasis was the effect of the hypercalcemia, not the cause. Because nine of the cats with urolithiasis were in renal failure, the renal failure group could be expanded to include at least 27 cats (38 per cent). Six additional cats with neoplasia had renal failure, but the cause of the hypercalcemia could not be determined. No definable cause of hypercalcemia was identified in 18 per cent of affected cats.[28]

Hypercalcemic cats have parathyroid-independent hypercalcemia much more commonly than dogs. Approximately 80 per cent of samples from 332 hypercalcemic cats sent to a veterinary endocrine diagnostic laboratory were categorized as parathyroid-independent, 10 per cent were parathyroid-dependent, and 10 per cent were equivocal.[16] Approximately 10 per cent of the 332 hypercalcemic cats had PTHrP levels above the reference range, suggesting malignancy as the cause. In comparison, in samples from 5722 hypercalcemic dogs from the same laboratory, 40 per cent were categorized as parathyroid-dependent hypercalcemia, 50 per cent were parathyroid-independent, and 10 per cent were equivocal.[33]

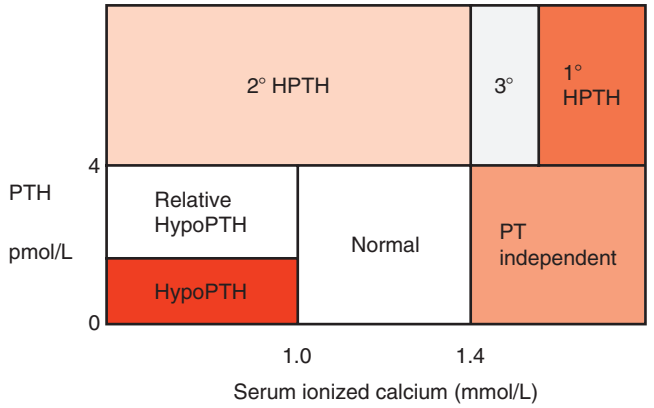

Figure 17-3. Relationship of expected serum PTH concentration (pmol/L) and ionized calcium concentration (mmol/L) with calcium disorders in cats. *2°HPTH,* Secondary hyperparathyroidism; *3°HPTH,* tertiary hyperparathyroidism; *1°HPTH,* primary hyperparathyroidism; *HypoPTH,* hypoparathyroidism; *PT independent,* parathyroid independent hypercalcemias. Note: Some cats with primary hyperparathyroidism may have a serum PTH concentration in the upper half of the normal range.

In some cats with persistent hypercalcemia, the cause of hypercalcemia is obvious after analysis of history (e.g., exposure to vitamin D, or certain drugs or house plants) or from physical examination findings (e.g., masses, organomegaly, or granulomatous disease). In other cases, the cause is not obvious and information from hematology, serum biochemistry, body cavity imaging, cytology, and/or histopathology is necessary. Measurement of ionized calcium and PTH concentrations is important in patients in which a diagnosis is not apparent from the history and physical examination. If possible, serum PTH and PTHrP concentrations should be measured at this time. The chronicity of the hypercalcemia also may help to delineate the cause. It becomes increasingly unlikely that cats with months of nonprogressing or gradually worsening serum total hypercalcemia will have malignancy, especially in the presence of minimal to no clinical signs. The longer a cat lives with hypercalcemia, the more likely the diagnosis will be idiopathic hypercalcemia, CRF-associated hypercalcemia, or primary hyperparathyroidism.

No relationship has been found between the magnitude of hypercalcemia and observed clinical signs.[28] In one study of hypercalcemic cats, the magnitude of hypercalcemia was higher in those patients with malignancy (serum total calcium 13.5 ± 2.5 mg/dL) than in those with chronic renal failure (serum total calcium 11.5 ± 0.4 mg/dL).[28] The magnitude of hypercalcemia cannot be used reliably to make a diagnosis, because the degree of hypercalcemia that develops amongst those with the same condition varies widely. For example, although serum total calcium concentration elevation tends to be mild in cats with chronic renal failure (CRF), these patients occasionally have serum total calcium concentrations of 13 to 14 mg/dL. Some cats with idiopathic hypercalcemia have mild increases in total calcium concentration (serum total calcium 11 to 12 mg/dL), whereas others have a serum total calcium concentration in excess of 15 mg/dL or, in rare cases, 20 mg/dL.

Mild hypercalcemia often is overlooked or ignored by veterinarians. Some of these cats have mild or inapparent clinical signs, so the need for continued diagnostic vigilance may not be obvious to the owner or the veterinarian. The magnitude of hypercalcemia may remain static or may steadily increase unnoticed for long periods. The consequences of longstanding hypercalcemia can be devastating when chronic renal failure or calcium oxalate urolithiasis develops (especially if located in the kidneys or ureters) (see Chapters 41 and 43).

DISORDERS CAUSING HYPERCALCEMIA

Chronic Renal Failure

Chronic renal failure, as discussed above, is the disease associated most commonly with serum total hypercalcemia in cats.[26] The incidence of serum total hypercalcemia increases with the severity of azotemia. In 73 cats with CRF, serum total calcium was increased in 8 per cent, 18 per cent, and 32 per cent of those with mild, moderate, or severe azotemia, respectively.[13] When present, CRF-associated total hypercalcemia typically is mild, rarely increased above 12 mg/dL (3 mmol/L).[13,34] On the other hand, the frequency of hypercalcemia in cats in renal failure is unknown. In cats with CRF, the reported incidence of serum total hypercalcemia ranges from 11.5 per cent[34] to 58 per cent,[13] depending on the population of cats studied.

A higher percentage of cats with CRF have elevations of serum total calcium as compared with an elevation of ionized calcium, possibly because of an increase in the complexed calcium fraction with CRF as has been noted in dogs.[35] Overall, in the presence of CRF, cats seem to have a higher incidence of ionized hypercalcemia than do dogs. Thirty of 104 cats (29 per cent) with CRF had an ionized hypercalcemia,[5] compared to 44 of 490 dogs with CRF (9 per cent).[36] As compared with total serum calcium concentrations, increases in ionized calcium do not show a strong association with degree of azotemia.[37] In 47 of the previously mentioned 73 cats with CRF, ionized calcium was increased in 0 per cent, 9 per cent, and 6 per cent of those with mild, moderate, or severe azotemia, respectively.[13]

Because the frequency of ionized hypercalcemia is higher in cats with CRF than in dogs, it is even more important to measure ionized calcium in cats with CRF that are discovered to have total serum calcium concentrations at the high end of the reference range or above. In one study, approximately one third of cats with CRF had diagnostic discordance between serum total calcium and ionized calcium.[5] Therefore it is impossible to determine if hypercalcemia requires treatment when hypercalcemia is diagnosed by serum total calcium measurement. If the ionized calcium is within the reference range or below, serum total hypercalcemia is not dangerous to the cat or to the kidneys; however, if ionized calcium is increased along with the serum total calcium, then hypercalcemia is dangerous. CRF is a possible end-point from longstanding or severe ionized hypercalcemia of any cause, so untreated ionized hypercalcemia can cause further renal damage.

In a patient being examined for the first time that has both ionized hypercalcemia and CRF, a diagnostic dilemma exists. As a result of the interplay between calcium, PTH, and CRF, it can be difficult or impossible to determine if the ionized hypercalcemia or the CRF developed first. If the serum ionized calcium concentration is increased in cats with CRF, all differential diagnoses for ionized hypercalcemia must be entertained. Ionized hypercalcemia can cause CRF, but CRF also can create ionized and nonionized hypercalcemia. In addition, CRF can lead to secondary or tertiary hyperparathyroidism. Tertiary

hyperparathyroidism is a rare condition in which ionized hypercalcemia emerges over months to years in cats with CRF, as a consequence of transformation from renal secondary hyperparathyroidism. With tertiary hyperparathyroidism, PTH levels will be increased inappropriately compared with the serum calcium concentration. In tertiary hyperparathyroidism, the continual secretion of PTH may lead to the down-regulation of the effects of calcitriol on the parathyroid gland, and the calcium setpoint for the release of PTH is altered. In general, in cats with CRF and subnormal or normal PTH concentrations along with mild unchanging or gradually worsening mild ionized hypercalcemia, the diagnosis likely will be idiopathic hypercalcemia. Cats with CRF and tertiary hyperparathyroidism also may have a gradually increasing ionized calcium concentration, but with concomitantly rising PTH concentrations. Lastly, in a cat with CRF and ionized hypercalcemia, a diagnosis of aluminum intoxication should be considered, although these cats closely resemble all features of idiopathic hypercalcemia.

Idiopathic Hypercalcemia

Within the past 10 years, idiopathic hypercalcemia has been recognized as a diagnostic consideration for cats with hypercalcemia.[17,18] Its frequency of diagnosis continues to increase, and it now may be the most common cause of ionized hypercalcemia in cats in the United States. Although it has been suggested that idiopathic hypercalcemia is a local geographical phenomenon,[19] it is widespread across the United States.[14] Reports of idiopathic hypercalcemia in cats also are emerging from several other parts of the world (anecdotes from England, Scandinavia, and Switzerland, especially).

With idiopathic hypercalcemia, serum calcium concentration often is increased for months to more than 1 year without obvious clinical signs. Hypercalcemia commonly is a fortuitous discovery from blood samples taken for other reasons (e.g., preanesthesia, geriatric screening, unrelated vomiting episode that often has resolved). In 427 cats with idiopathic hypercalcemia diagnosed at a single diagnostic laboratory, no obvious clinical signs were noted in nearly half of these cases (46 per cent). In addition, 18 per cent had mild weight loss only, 5 per cent were chronically constipated, 4 per cent were vomiting, and 1 per cent were anorectic.[30] Uroliths or renoliths were observed in 15 per cent, and calcium oxalate stones were noted specifically in 10 per cent. Interestingly, this distribution of clinical signs is different from that gleaned from the earlier literature (see Table 17-2). Two explanations exist for the difference. First, the clinical signs associated with idiopathic hypercalcemia may not be the same in relative frequencies as those seen with other causes of hypercalcemia attributable to underlying inherent variation in disease process, such as magnitude of hypercalcemia, rate of rise in serum calcium concentration, or hormonal alterations. Alternatively, the information on the 427 cats with idiopathic hypercalcemia was derived from information supplied to a diagnostic laboratory, and all pertinent data may not have been provided.

The etiopathogenesis of idiopathic hypercalcemia in cats is unknown. In the 427 cats noted above, the cats ranged in age from 0.5 to 20 years old (mean 9.8 ± 4.6 yr), and long-haired cats were overrepresented, accounting for 27 per cent of the cases (compared with an overall submission rate of 14 per cent from long-haired cats). Males and females were represented equally. Serum ionized calcium concentration was increased in all cats, mean PTH concentration was in the lower half of the reference range, and PTHrP was negative in all samples. Ionized magnesium concentration also was within the reference range.[30] In another study, two of 11 cats had an increased serum PTHrP concentration in the absence of evidence for underlying neoplasia after extensive diagnostic evaluation, survival for many months, and necropsy.[18] Therefore, idiopathic hypercalcemia apparently is not due to excessive PTH concentrations in cats. Undetected neoplasia is unlikely based on PTHrP measurements and results from abdominal and thoracic radiography, abdominal ultrasonography, bone marrow evaluation, and in some instances, full necropsy**.** Normal ionized magnesium concentrations indicate that PTH secretion is not being inhibited by alterations in ionized magnesium.[30]

Some investigators have speculated that idiopathic hypercalcemia in cats is a consequence of too much dietary vitamin D (cholecalciferol), despite normal serum 25-hydroxyvitamin D concentrations. In the series of 427 cats with idiopathic hypercalcemia, mean serum concentration of 25-hydroxyvitamin D was within the reference range and a few cats had a trivially elevated concentration. Mean calcitriol concentration was suppressed in a small number.[27] Only one of seven cats in another study had an increased serum calcitriol concentration.[15]

Although normal values for serum or plasma concentrations of 25-hydroxyvitamin D have been established for cats ingesting vitamin D–supplemented diets, the minimal requirement for dietary vitamin D intake in cats is debatable. However, it is unlikely that normal plasma 25-hydroxyvitamin D concentrations would induce hypercalcemia. Increased vitamin D sensitivity seems unlikely because levels of the most active vitamin D metabolite, 1,25-dihydroxyvitamin D (calcitriol), are not expected to rise even if increased amounts of 25-hydroxyvitamin D are provided as substrate. The hydroxylase enzyme system within proximal renal tubular cells is under tight regulatory control for the conversion of 25-dihydroxyvitamin D to calcitriol, and if intrarenal enzymes respond normally to physiological concentrations of 25-hydroxyvitamin D, increased conversion to calcitriol is not expected. Cats with idiopathic hypercalcemia have been documented rarely to have increased 1,25-dihydroxyvitamin D concentrations; therefore increased conversion of 25-hydroxyvitamin D to calcitriol is an unlikely mechanism for hypercalcemia. However, normal concentrations of calcitriol potentially could be associated with hypercalcemia if a mutation of the vitamin D receptor increases receptor activity, if the activity of the vitamin D receptor is changed by other factors in the cat's body, or if numbers of calcitriol receptors are increased. These possibilities have not been investigated at this point.

The relationship between CRF and idiopathic hypercalcemia is less clear. Some cats develop CRF secondary to longstanding idiopathic hypercalcemia, whereas conversely, some cats with CRF develop idiopathic hypercalcemia after protracted periods of normocalcemia. A third population is diagnosed concurrently with both CRF and idiopathic hypercalcemia.

The cause(s) of feline idiopathic hypercalcemia remains elusive. The role of dietary acidification, dietary magnesium restriction, and/or contribution of any specific dietary constituents deserves further consideration. Hypercalcemia possibly may develop only in a genetically susceptible population of cats in a provocative environment (e.g., diet, toxins,

environment, or stress). A genetic component seems likely, given the overrepresentation of long-haired cats. Studies should focus on determining whether enhanced intestinal calcium absorption or bone resorption, or decreased renal calcium excretion, are present. Other conditions that have not received much attention to date for a possible role in the pathophysiology of idiopathic hypercalcemia include aluminum intoxication (especially in those patients in which hypercalcemia emerges while on aluminum-containing intestinal phosphate binders), hypervitaminosis A (retention may be a problem in cats with diminished renal function), adrenal gland hypofunction, and compensatory acid-base responses to chronic feeding of acidifying and magnesium-restricted diets. Novel basic mechanisms, such as the presence of a PTH or vitamin D mimetic, calcium receptor antagonist, bone resorption promoter, and/or intestinal calcium absorption stimulator, may be operative in the pathophysiology of idiopathic hypercalcemia.

Malignancy-Associated Hypercalcemia

A number of tumors have been associated with hypercalcemia in cats, including lymphosarcoma,[28,38-40] multiple myeloma,[41-43] squamous cell carcinoma,[28,44,45] bronchogenic carcinoma/adenocarcinoma,[16,28,29] osteosarcoma,[28] fibrosarcoma,[28] undifferentiated sarcoma,[28] undifferentiated renal carcinoma, anaplastic carcinoma of the lung and diaphragm, and thyroid carcinoma.[16] Lymphosarcoma and squamous cell carcinoma are the two most common, each accounting for approximately 33 per cent of cases of malignancy-associated hypercalcemia.[28] No single anatomical location of lymphosarcoma has been determined to be more likely to cause hypercalcemia in cats. Of 11 cats with lymphosarcoma reported to be hypercalcemic, two cats each had renal,[28] generalized,[28,40] gastrointestinal,[16,28] or mediastinal[28,39] involvement, and one had laryngeal, nasal,[28] or cutaneous disease.[38] Locations for squamous cell carcinoma have been mandibular,[28,45] maxillary,[44] pulmonary,[16] and within the ear canal.[28] One cat with hypercalcemia from squamous cell carcinoma had multifocal metastatic cutaneous squamous carcinomas in lungs, heart, kidneys, and skeletal muscles.[44]

Upon careful examination, masses of the head and neck (mandible, mouth, ears) will be obvious if the hypercalcemia is caused by squamous cell carcinoma. Peripheral lymphadenopathy is not common in those patients with lymphosarcoma, but organomegaly and/or mediastinal lymphadenopathy will be identifiable in most cases after palpation, radiography, or ultrasonography. Bone marrow aspirate may be needed to confirm lymphosarcoma or other myeloproliferative disorder, especially if peripheral cytopenias are present. Positive feline leukemia virus (FeLV) serology was reported in most early reports from cats with hypercalcemia and lymphosarcoma, but only one of seven cats was FeLV-positive in a later report.[28]

On endocrine testing of cats with humoral hypercalcemia of malignancy, ionized calcium is elevated, PTH is within the lower half of the reference range or undetectable, and 25-hydroxyvitamin D and calcitriol concentrations are normal. Serum PTHrP concentration may be elevated but can be undetectable, because malignancy-associated hypercalcemia may be due to synthesis of other cytokines by the tumor. All masses should be aspirated and evaluated cytologically or biopsied for definitive diagnosis.

Primary Hyperparathyroidism

Primary hyperparathyroidism has been reported in 20 cats.[19-23,25,28] The underlying lesion typically is benign, being either an adenoma,[19,20,22,23,28] bilateral cystadenomas,[20] or hyperplasia,[25,28] but unilateral or bilateral carcinomas do occur.[19-21,24] In a recent report of hypercalcemic cats, primary hyperparathyroidism was diagnosed as the cause in four of 71 (6 per cent) cases.[28] Clinical signs are consistent with hypercalcemia of any cause. Calcium-containing stones have been reported to form in some cats with primary hyperparathyroidism. Unlike dogs, an enlarged parathyroid gland(s) may be palpable in cats with primary hyperparathyroidism.

On endocrine testing, primary hyperparathyroidism is characterized by an elevation in serum total and ionized calcium concentration in association with an inappropriately elevated serum PTH concentration (parathyroid-dependent hypercalcemia). A serum PTH concentration above the reference range in association with hypercalcemia and normal renal function provides definitive evidence for the diagnosis. Because PTH production and secretion should be suppressed in a cat with hypercalcemia and normal parathyroid function, a PTH concentration at the upper limit of the reference range in a hypercalcemic cat with normal renal function may still suggest the presence of primary hyperparathyroidism. Serum PTH concentration varies over time. In a cat with documented hypercalcemia and parathyroid gland adenoma of one case report, five of seven PTH measurements were within the normal range and two clearly were increased; of those within the normal range, all were above the median value for the range.[22] Increased serum alkaline phosphatase activity may be attributable to the effects of PTH on bone. Hypophosphatemia also may be present.

Ultrasonographic evaluation of the parathyroid glands in hypercalcemic cats has been reported uncommonly. A cystic lesion associated with a parathyroid gland adenocarcinoma in a cat was diagnosed using ultrasonography.[24] In addition, parathyroid gland adenomas greater than 1.0 cm diameter were identified ultrasonographically in two cats. Both masses contained hypoechoic areas with distal acoustic enhancement.[23]

Hypervitaminosis D

Hypervitaminosis D refers to activity of excess concentrations of vitamin D metabolites including ergocalciferol, cholecalciferol, dihydrotachysterol, calcitriol, and calcitriol analogues including calcipotriene. In general, there are few reports of vitamin D toxicity in cats, however, because cats appear to be resistant to cholecalciferol toxicity when the diet is otherwise complete and balanced.[46]

Toxic effects of ergocalciferol and cholecalciferol during treatment for hypoparathyroidism often result in hypercalcemia. Because the time for maximal effect and duration of action is relatively long and unpredictable for these compounds, determination of an optimal dose can be difficult. Oversupplementation with vitamin preparations containing vitamin D could account for hypercalcemia in rare instances. Vitamin D toxicity secondary to ingestion of cholecalciferol-containing rodenticide ingestion has been reported in only four cats,[26,27] and use of these rodenticides has decreased in the United States since initial reports detailed hypercalcemia in dogs and cats. Ingestion of vitamin D–containing plants such

as day-blooming jessamine (*Cestrum diurnum*) has been associated with hypercalcemia; ingestion of other plants (*Solanum malacosylon*, a member of the nightshade family, and *Trisetum flavescens,* yellow oatgrass) also poses a potential risk. Hypervitaminosis D resulting in adverse clinical signs, hypercalcemia, azotemia, high concentrations of 25-hydroxyvitamin D, and/or renal calcification has been described in three reports of cats from Japan eating commercial cat food consisting of fish. Cholecalciferol content of these diets ranged from 52,900 to 67,300 IU/kg of diet.[48-50] According to the National Research Council (NRC)[51] the minimal requirement for vitamin D for growing cats is 500 IU/kg of diet, but one study suggested that 125 IU/kg of diet is sufficient.[52] All commercial cat foods provide vitamin D in excess of the minimal requirements, but most companies do not routinely measure or provide information regarding the actual vitamin D content in their products because of expense and difficulty in the measurement. The quantity of vitamin D that can be included in the diet is not restricted, and in general, diets formulated with large amounts of salt-water fish have a higher vitamin D content. In one report, some diets exceeded the 1986 NRC recommendation for vitamin D content by a factor of 55, and many canned foods consisting predominantly of marine fish exceeded the minimal requirement by a factor of 30.[53] Feeding of a commercial cat food containing 15,000 IU cholecalciferol/kg of diet resulted in renal disease and renal failure within 4 to 14 months in a large number of study cats.[54] In a study of kittens and queens consuming a diet containing 30,000 IU cholecalciferol/kg of diet for 18 months, even though plasma cholecalciferol increased by a factor of 10 and 25-hydroxyvitamin D increased by a factor of five, serum total calcium concentration increased slightly but was still within the reference range. In addition, hyperphosphatemia did not develop either, as occurred in other reported cases of hypervitaminosis D. Other factors that may modulate the toxicity of hypervitaminosis D are increased dietary calcium and phosphorus, and dietary reduction in magnesium.[46]

Daily treatment with calcitriol for control of renal secondary hyperparathyroidism rarely results in hypercalcemia when low doses are used; when hypercalcemia is observed, it usually is in patients administered doses greater than 3.5 ng/kg daily. Because no veterinary calcitriol formulation exists, available preparations are compounded by diluting calcitriol in pharmaceutical oils, and formulation errors have been encountered occasionally in which the concentration of calcitriol in a compounded product was too high. Such mistakes should be considered as a cause of hypercalcemia if it develops in a cat receiving calcitriol for control of renal secondary hyperparathyroidism. Hypercalcemia also has been encountered when dosing errors have been made (mg/kg amounts given as opposed to ng/kg amounts).

Calcipotriene is a topical dermatological calcitriol analogue prescribed for treatment of psoriasis in human beings. Calcipotriene-induced hypercalcemia has not been reported in the literature in cats as in dogs.[55] Anecdotally, however, two cats (one in Ireland and one in Australia) have developed hypercalcemia after licking calcipotriene from their owner's skin.[56]

Granulomatous diseases have the potential to cause hypercalcemia in cats as a consequence of the ability of macrophages to biosynthesize calcitriol from 25-hydroxyvitamin D without negative feedback regulation. Granulomatous disease attributable to histoplasmosis,[57] *Nocardia* spp., and atypical mycobacteria[58] was considered to be the cause of hypercalcemia in two of eight cats, two cats, and one cat, respectively. Elevated calcitriol concentrations were documented in the cases of *Nocardia* spp. and atypical mycobacteria infection.[58] Cats with blastomycosis[59] and injection-site granulomas[60] (personal communication Mark Peterson, 2002) have been noted to be hypercalcemic, possibly because of enhanced calcitriol synthesis.[61] Whether or not hypercalcemia develops in patients with granulomatous disease is a function of the extent of the granulomatous reaction and the number of activated macrophages, because most cats with granulomatous inflammation do not become hypercalcemic.

Each of four hypercalcemic cats also have been found to have feline infectious peritonitis, toxoplasmosis, pulmonary cryptococcosis, or severe chronic *Actinomyces* rhinitis,[28] but a causal relationship was not clearly established. The cats with feline infectious peritonitis and toxoplasmosis also had diabetes mellitus,[28] which may have contributed to measurement of hypercalcemia.

Results of diagnostic testing in patients with vitamin D toxicity vary somewhat depending on the form of vitamin D to which the patient was exposed. In all forms of vitamin D toxicosis, PTH concentrations are suppressed to within the lower part of the reference range or are undetectable, and PTHrP concentrations should be undetectable. Following exposure to excess ergocalciferol or cholecalciferol, serum concentrations of 25-hydroxyvitamin D will be elevated for weeks to months because of lipid storage and slow release. Calcitriol concentrations usually are within the reference range but can be increased in some patients. With calcitriol toxicity, 25-hydroxyvitamin D concentration will be normal; calcitriol concentration may be elevated or also may be normal because the plasma half-life is short, but biological activity may remain for several days. With calcipotriene exposure, 25-hydroxyvitamin D concentration will be normal. Whether this compound cross-reacts with and is detected by an assay for calcitriol has yet to be determined.

Hyperthyroidism

Recently, serum total hypercalcemia was noted in two of 26 (8 per cent)[62] and two of 71 (3 per cent) hyperthyroid cats.[28] In one study, the serum ionized calcium concentration was measured and was normal in both cats,[62] and therefore the elevation in serum total calcium concentration was not significant. In comparison, mild ionized hypercalcemia that resolved after restoration of euthyroidism with iodine-131 treatment has been noted uncommonly in untreated hyperthyroid cats.[63] The importance of this observation remains to be determined.

Hypoadrenocorticism

Naturally occurring hypoadrenocorticism (Addison's disease) is a rare endocrinopathy in cats, and hypercalcemia occurs in only 8 per cent of cases.[64] Hypercalcemia also was present in one cat with iatrogenic secondary hypoadrenocorticism and diabetes mellitus.[65] Thus in cats with hypercalcemia, hypoadrenocorticism is not likely to be the cause. In one study, only one of 71 cats (1 per cent) with total serum hypercalcemia was diagnosed with hypoadrenocorticism.[28] Hypercalcemia abates rapidly during treatment and does not likely contribute to the pathophysiology of this disorder, although its presence can be suggestive of a diagnosis of hypoadrenocorticism.

Cats with idiopathic hypercalcemia have not been evaluated systematically for the presence of adrenal gland hypofunction. Because these cats do not have alterations in serum sodium or potassium concentrations, hypoadrenocorticism with cortisol and mineralocorticoid deficiency (i.e., "typical" hypoadrenocorticism) often is not suspected, and ACTH stimulation testing to document adrenal abnormalities is not performed. Because glucocorticoid deficiency alone does not affect sodium or potassium concentrations, cats with idiopathic hypercalcemia may have undiagnosed diminished adrenal cortisol secretion. However, adrenal gland abnormalities have not been reported in cats with idiopathic hypercalcemia that have undergone necropsy. Future evaluation of cats with idiopathic hypercalcemia should include ACTH stimulation testing to evaluate adrenal function, in addition to CT to determine adrenal gland volume.

Miscellaneous Causes of Hypercalcemia

Other diseases have been reported to cause hypercalcemia. Hypothermia caused hypercalcemia in one cat.[47] One cat with pancreatitis and hypercalcemia has been described; however, hypocalcemia is more common in cases of pancreatitis.[66] One cat exhibited hypercalcemia post–renal transplantation[67]; however, this cat also had a parathyroid gland adenoma, and it is likely that hypercalcemia was exposed when a new kidney that could synthesize calcitriol was provided and hyperphosphatemia resolved. Dehydration should be considered as a cause for mild and reversible hypercalcemia, especially in the face of normal kidney function, in which volume contraction stimulates renal tubular reabsorption of both sodium and calcium.

TREATMENT OF HYPERCALCEMIA

Emergency Treatment

Treatment for hypercalcemia is necessary only if ionized hypercalcemia exists and is best accomplished by addressing the underlying disorder. Therefore the cause should be delineated as quickly as possible and appropriate therapy instituted. The need for aggressive treatment aimed specifically toward resolving hypercalcemia is based on severity of clinical signs and magnitude of the hypercalcemia.[1] Hypercalcemia can be damaging, especially to the kidneys, with severity dependent on the phosphorus concentration. If the product of multiplying the serum total calcium concentration by the serum phosphorus concentration is greater than 70, nephrotoxicity is likely. If the etiology cannot be identified rapidly and continuing hypercalcemia is judged to be deleterious (e.g., renal function is declining, $Ca \times P > 70$, dehydration exists), if clinical signs are severe (e.g., depression, anorexia, vomiting, encephalopathy, arrhythmia), or if the hypercalcemia is idiopathic, the hypercalcemia should be addressed directly.

The first step in symptomatic treatment is to provide intravenous fluids to correct dehydration.[1] The resulting volume expansion dilutes the circulating calcium concentration and increases renal calcium excretion. The fluid of choice is 0.9 per cent sodium chloride solution, because the sodium floods the nephrons, competing for sites of renal tubular calcium absorption. Often a fluid volume infusion of two to three times maintenance requirements (120 to 180 ml/kg/day) corrects dehydration and provides maintenance needs and mild volume expansion. Treatment with intravenous fluids alone lowers the degree of hypercalcemia, but will not decrease the concentration into the reference range if hypercalcemia is severe.

Furosemide is added to the intravenous fluid regimen when hypercalcemia has not resolved, dehydration has been corrected, and clinical signs are still severe. An experimental regimen of treating with a bolus of furosemide followed by constant rate infusion has been developed for dogs[68] but creates extensive diuresis with potential dehydration. Dehydration is undesirable because hemoconcentration offsets any benefits from calciuresis. As an alternative, intermittent furosemide (1 to 2 mg/kg q8-12h) often is used in dogs to minimize dehydration. Aggressive use of furosemide is not employed often in cats with hypercalcemia.

Calcitonin has been used uncommonly to treat hypercalcemia in cats. If used, it is added to the treatment regimen (4 to 6 IU/kg SQ q8-12h) in those patients in which intravenous fluids and furosemide administration has not resolved the hypercalcemia. Calcitonin has a quick onset of action, although the magnitude and duration of effect are limited. Whether cats receiving calcitonin may become anorectic, as encountered in some dogs, is not known.[69]

Intravenous fluids, furosemide, and calcitonin are quick-acting treatments to lower the magnitude of hypercalcemia. If control of hypercalcemia is needed for a longer period (if the primary cause cannot be removed), use of an intravenous bisphosphonate may be helpful if the hypercalcemia results from osteoclastic bone resorption. These agents may need a few days to exert maximal effects, and therefore treatment should be initiated at the same time as quicker acting agents. The successful use of intravenous bisphosphonates has been reported recently for the treatment of hypercalcemia in two cats, one with nocardiosis and one with idiopathic hypercalcemia.[70] Treatment with oral bisphosphonates has not been reported in cats. Oral bisphosphonates are used extensively in the treatment and prevention of osteoporosis in women; however, erosive esophagitis is a potential side effect.[71] Whether oral bisphosphonates can be administered safely and effectively to cats with hypercalcemia remains to be determined. Until safety studies have been completed, the use of oral bisphosphonates in cats cannot be recommended.

Glucocorticoids decrease the magnitude of hypercalcemia by decreasing intestinal calcium absorption, decreasing renal tubular calcium reabsorption, and reducing bone resorption. Dramatic reduction of calcium concentration often occurs with glucocorticoid therapy in patients with lymphosarcoma, multiple myeloma, hypoadrenocorticism, or hypervitaminosis D. A dramatic reduction in magnitude of hypercalcemia also is seen in some cats with idiopathic hypercalcemia. Withholding glucocorticoid therapy until all diagnostic testing has been performed is best, however, because glucocorticoid administration may obscure the presence of a disease and make reaching a definitive diagnosis impossible.

Maintenance Therapy

If clinical signs are minimal, chronic management to reduce the magnitude of hypercalcemia is adequate. Treatment should be pursued, because renal damage may occur with longstanding hypercalcemia. Subcutaneous fluids help maintain hydration and minimize the magnifying effects of hemoconcentration. Benefits of oral furosemide must be weighed against the

potential to create dehydration. Furosemide therapy must be discontinued in those cats that fail to increase water intake as urine volume increases.

In cats with CRF and ionized hypercalcemia, therapy should be instituted and directed towards the various nonrenal causes of hypercalcemia. Changing the diet to one that is less phosphorus-restricted should be considered. Two of 15 clinical cats fed a diet designed for cats with CRF developed hypercalcemia in the face of suppressed serum PTH concentrations, possibly attibutable to a reduction of phosphate load in the body. The hypercalcemia resolved when a maintenance diet was reintroduced.[72] A diagnosis of aluminum intoxication should be considered in cats receiving aluminum salt intestinal phosphate binders, although these cats closely resemble all features of idiopathic hypercalcemia. With aluminum intoxication, removal of aluminum-containing phosphate binders should eventually result in resolution of hypercalcemia, but resolution may take months attributable to bone stores of aluminum. Newer generation phosphate binders such as sevelamer hydrochloride and lanthanum carbonate do not contain aluminum, but we have little experience with these drugs, and there are no data on safety or efficacy in cats. Lastly, if hypercalcemia develops in cats receiving calcium-containing intestinal phosphate binders, their administration should be stopped and another class of phosphate binder chosen. Development of hypercalcemia is more common with the administration of calcium carbonate as compared with calcium acetate. The tendency to develop hypercalcemia while receiving calcium salts is magnified if the patient is receiving calcitriol concurrently for the control of renal secondary or tertiary hyperparathyroidism.

Because the pathogenesis of idiopathic hypercalcemia remains unknown, the rational approach for treatment of addressing the underlying mechanism or disease is impossible. Increased bone resorption, increased intestinal calcium absorption, or decreased renal calcium excretion (increased tubular reabsorption or decreased glomerular filtration) could be operative alone or in combination. Empirical treatments, however, have proven effective for some cats with idiopathic hypercalcemia. Feeding of increased dietary fiber has decreased serum calcium concentration in some cats with idiopathic hypercalcemia,[17] but not in others.[18] The salutary effect of a higher fiber diet may be attributed to decreased intestinal calcium absorption, but this has not been studied. The effects of fiber on intestinal absorption are complex, and depend on the types and amount of fiber and other nutrients present in the diet.

Feeding of diets designed for cats with CRF also may result in normocalcemia in some cats with idiopathic hypercalcemia, possibly as a result of the reduced dietary calcium content. Veterinary renal diets generally are low in calcium and phosphorus, and calcium restriction generally is more severe in canned as compared with dry renal diets. In addition, renal diets are considered alkalinizing or, at least, less acidifying than maintenance diets. Beneficial effects from the feeding of a renal diet for treatment of idiopathic hypercalcemia could result from decreased dietary calcium intake with subsequently decreased intestinal calcium absorption, or possibly from the effects of alkalinization, which can decrease calcium release from bone. Some concern exists, however, that veterinary renal diets may enhance renal synthesis of calcitriol as a result of the effects of dietary phosphate restriction, which could offset the potential advantages of the initial lower intestinal calcium absorption.

Some cats that have an initial decline in serum calcium concentration after a dietary change to either a renal or a high fiber diet will have a return to hypercalcemia after variable periods of time. Other components of the diet not traditionally considered important in calcium dynamics may exert unsuspected effects. For example, in one study, rats were fed identical diets with the exception of either 30 per cent dietary lactose or sucrose. Feeding of the lactose-enriched diet resulted in increased serum total calcium concentration, increased 24-hour urinary calcium excretion, increased urinary citrate excretion, and increased calcium oxalate dihydrate crystalluria with stable effects on glomerular filtration for at least 8 weeks.[73]

In some cats with idiopathic hypercalcemia that do not respond to a dietary change, prednisone therapy can result in long-term decreases in ionized and total serum calcium. Although the effects of glucocorticoid administration on renal tubular calcium reabsorption in cats are unknown, concern exists that prednisone administration could increase hypercalciuria as a result of decreased tubular calcium reabsorption as occurs in dogs; the enhanced urinary calcium excretion could, in turn, enhance genesis of calcium-containing urinary calculi. However, the filtered load of calcium would decrease as serum ionized calcium concentration declines, which may offset the enhanced formation of calculi from the tubular effects. For cats with idiopathic hypercalcemia that respond to glucocorticoid administration, the beneficial effects may last for months to years with ongoing medication at doses of 5 to 20 mg/cat/day. However, an escape from the effect of glucocorticoid treatment occurs in some affected cats, and hypercalcemia returns despite maximal prednisone doses.

When dietary modification and treatment with prednisone are unsuccessful in resolving idiopathic hypercalcemia, bisphosphonate treatment can be considered. We have limited experience with bisphosphonates in cats, although we have used pamidronate intravenously in cats successfully as developed for use in dogs. Consideration of oral bisphosphonates such as alendronate may be tempting, but no reports of its safety or efficacy exist in cats.

Other treatments exist that may be valuable but are unproven. Although fluid and/or furosemide administration are advocated for emergency treatment of hypercalcemia, possible benefits of chronic administration of subcutaneous fluids or oral furosemide to cats with idiopathic hypercalcemia have not been evaluated. Treatment of hypercalcemia with a new generation of drugs called calcimimetics has emerged recently in human medicine. Calcimimetics were designed to interact with calcium receptors and lower serum calcium, phosphorus, and PTH concentrations effectively in human patients undergoing dialysis, in whom phosphorus binders and calcitriol or calcitriol analogues were not efficacious in controlling renal secondary hyperparathyroidism.[74] Calcimimetics also have been used to control primary hyperparathyroidism as an alternative to surgery.[75,76] Whether this class of drugs will have a role in the management of idiopathic hypercalcemia in cats is not yet known, but their potential use for this problem is intriguing.

Treatment of hypervitaminosis D depends on the form of vitamin D that caused the problem. If hypercalcemia occurred secondary to calcitriol ingestion, discontinuation of calcitriol should result in normocalcemia within 1 week. If the calcitriol was being administered to treat renal secondary hyperparathyroidism, reinstituting the calcitriol with every-other-day dosing at twice the daily dosage upregulates fewer intestinal epithelial

cells for calcium absorption and decreases the chance for further development of hypercalcemia. For calcipotriene toxicity in dogs, pamidronate has been used and may be helpful in cats (see above). Similarly, bisphosphonates also may be beneficial in treatment of cholecalciferol or ergocalciferol toxicity.

For primary hyperparathyroidism, surgery is preferred for removal of the affected gland(s). Alternatively, ethanol injection or radiothermy treatment of the enlarged parathyroid gland can be considered for selected cases. For humoral hypercalcemia of malignancy, tumoral control should be sought by whatever means is recommended for the particular neoplasm. The hypercalcemia should resolve for as long as the tumor is in remission. For granulomatous disease, surgery may be an option for local lesions, or systemic therapy may be required for widespread disease.

Dietary restriction of calcium is predictably helpful to minimize the magnitude of hypercalcemia in cats with hypervitaminosis D and resultant enhanced intestinal absorption of dietary calcium. Some cats with idiopathic hypercalcemia may respond to either increased dietary fiber or a veterinary renal food as described above. Restriction of dietary calcium is of no benefit when hypercalcemia is generated from the effects of malignancy. In these instances, hypercalcemia is maintained from increased bone resorption and renal tubular calcium reabsorption; intestinal calcium absorption already is low because of the suppression of PTH and calcitriol.

SUMMARY

Hypercalcemia traditionally has been considered an uncommon finding in cats, but this has changed dramatically over the past 10 years. Hypercalcemia has many potential etiologies, and a careful history, complete physical examination, and selective laboratory testing are necessary to determine the cause. The most common causes of hypercalcemia include idiopathic hypercalcemia, malignancy, and renal failure. Treatment is aimed at removal of the underlying cause of hypercalcemia if possible. The underlying mechanisms involved in idiopathic hypercalcemia must be elucidated before specific therapy can be recommended.

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Chapter 18

TRANSDERMAL THERAPEUTICS

Lauren A. Trepanier

The transdermal delivery of drugs to the systemic circulation has been in use for more than 25 years.[1] Transdermal nitroglycerin and scopolamine first were developed to bypass the problems of variable bioavailability, short duration of action, and side effects seen after oral administration.[2,3] Since then, a large number of drugs have been developed for transdermal administration in human beings, including fentanyl, contraceptives, hormonal replacement therapy, nicotine, oxybutynin, clonidine, and testosterone. Although nitroglycerin ointment has been in use for veterinary patients for decades, only recently have veterinary transdermal formulations been available for a wide variety of drugs through custom compounding pharmacies. For the vast majority of these formulations, however, absorption and efficacy data are absent, and clinicians should keep a clear view of the pros and cons of transdermal delivery when considering this route of administration.

TRANSDERMAL VERSUS TOPICAL ROUTES OF ADMINISTRATION

The transdermal administration of drugs, when medications are applied to skin with the goal of reaching therapeutic drug concentrations in the systemic circulation, is distinct from the topical administration of drugs, for which only local therapeutic drug concentrations in the skin or other surface organs (e.g., eye, mucous membranes) are necessary. For example, nonsteroidal antiinflammatory drugs (NSAIDs) can be delivered topically in human beings for local treatment of joint and muscle inflammation. Drugs can penetrate 3 to 4 mm at the site of application, with additional delivery to skin, muscle, and joint tissues though local blood supply.[4] Topical NSAIDs have been shown to be effective for local treatment of acute musculoskeletal injuries in most placebo-controlled studies in human beings, with minimal systemic side effects.[5]

Potential Advantages and Drawbacks of Transdermal Delivery

The transdermal route is intended to provide an alternative to oral or parenteral drug administration and offers both potential advantages and disadvantages (Table 18-1). One potential advantage of transdermal administration over oral administration is the ability to avoid first-pass clearance by the liver and gastrointestinal tract, which otherwise can lead to variable or low systemic drug concentrations. For example, isosorbide dinitrate achieves higher plasma concentrations in dogs by the transdermal route than by the oral route, presumably because of avoidance of first-pass clearance.[6] Another potential advantage of the transdermal route is the creation of a drug depot in the skin, which may allow slow release of drug over time, with lower peak drug concentrations but a longer duration of action. However, many drugs are not adequately absorbed transdermally, and those that are absorbed may not provide favorable pharmacokinetics.

Transdermal Formulations

Drugs to be delivered transdermally should be selected carefully and must be formulated appropriately. In general, small compounds (e.g., molecular weight less than 500 g) are better candidates for transdermal absorption than larger molecules.[7,8] In addition, properties such as a low melting point, low polarity, and relatively high lipophilicity contribute to enhanced absorption,[8,9] as do achievement of high local drug concentrations, and application across areas with relatively thin skin (e.g., pinnae, axillary and inguinal regions).

Veterinary drugs for transdermal administration typically are formulated in an emulsifying agent, solvent, or patch matrix to enhance absorption across the stratum corneum. One popular vehicle is pluronic lecithin organogel (PLO), which contains pluronic F127, a surfactant that forms drug micelles.[10] Lecithin increases the fluidity of the stratum corneum and causes low-grade exfoliation and inflammation with chronic use.[11,12] One disadvantage of PLO is that it separates in cold temperatures and therefore should not be refrigerated or shipped during very cold weather. PLO also is reported to have a "greasy" feel that is poorly accepted by some human patients. In comparison, Lipoderm (Professional Compounding Centers of America) is a proprietary vehicle that contains lecithin, but is less greasy than PLO and can be refrigerated.

Permeation enhancers also are included in transdermal formulations to increase drug delivery. PLO, lecithin, or pluronic F127 increase the permeation of many drugs, including insulin, theophylline, propranolol, and others, across mammalian skin

Table 18-1 | **Potential Advantages and Disadvantages of the Transdermal Route of Drug Administration**

FEATURE OF TRANSDERMALS	POTENTIAL ADVANTAGE	POTENTIAL DISADVANTAGE
Does not require oral administration or injections	May be better accepted by many cats	Some cats resent sensation of gel or patch
No direct gastric or intestinal contact	Decreased direct GI irritation	Inappropriate route for drugs acting locally in the GI tract
Avoids first pass oral biotransformation by the gut and liver	May avoid variable absorption seen with the oral route	May be inappropriate for pro-drugs dependent on biotransformation for efficacy
Absorbed slowly from depot formed in skin	May provide longer duration of action	May never reach therapeutic plasma concentrations
Avoids high peak plasma concentrations	May decrease acute dose-dependent side effects	Lack of immediate effect for most drugs needed in an emergency setting
Requires custom formulation	Concentration can be tailored to patient's size	Often more expensive than commercially available formulations; stability data often unavailable

or mucous membranes under experimental conditions.[13-15] Oleic acid, propylene glycol, ethanol, and glycol ethers also have been used.[16,17] Mechanisms for permeation enhancement include induction of a change in lipid fluidity in the stratum corneum, solubilization of lipids between corneocytes, generation of pores on the surface of corneocytes, or actual exfoliation of the stratum corneum.[16,18] Although DMSO is an efficient solvent for transdermal penetration of drugs, it is not used commonly in human beings because of its strong odor and potential for local irritation. Many other permeation enhancers also are irritating to skin, and therefore combinations of enhancers in lower doses have been used to decrease irritation that occurs with use of higher doses of any single agent.[19]

Another approach used to increase transdermal absorption in human beings is the formulation of polar drugs into "duplex pro-drugs" (two molecules of the drug linked by an ester bond). The duplex molecule often is more lipophilic and better absorbed across the stratum corneum, but then is cleaved locally by esterases in the skin to two molecules of the active parent drug. Naltrexone, used to treat alcohol and opiate dependence in human beings, has been delivered successfully using this approach.[20]

Transdermal patches also can be used to deliver a few specific medications. Commercially available transdermal patches are either "matrix-type" or "reservoir-type."[1] Matrix-type patches contain high concentrations of drug in a matrix or solvent, with one or more permeation enhancers. These patches rely on skin permeability to regulate drug delivery. Reservoir-type patches, such as the Duragesic fentanyl patch (Janssen Pharmaceutica, Titusville, NJ), are more complex, with an additional semi-permeable membrane that controls the rate of drug delivery.

Physical Disruption of the Stratum Corneum

All drugs formulated in patches and solvent systems for use in human beings are small (<500 g molecular weight), relatively lipophilic, and effective at low total daily doses. For delivery of larger or more polar molecules, physical disruption of the highly ordered lipid bilayers of the stratum corneum is necessary. One interesting strategy for this is the use of low-frequency ultrasound, a technique called sonophoresis.[21,22] For example, brief (10-second) pretreatment of the skin with low frequency ultrasound waves speeds the onset of action of EMLA cream (lidocaine/prilocaine) in human beings, which reduces the time needed for local analgesia from 60 minutes to only 5 minutes.[23] EMLA cream is safe in cats[24] but requires a 1-hour delay between application and scheduled procedures such as jugular catheterization,[25] arterial blood gas measurement, skin biopsy, or glucose curves. Sonophoresis could increase the practicality of EMLA cream analgesia in veterinary patients and deserves further study.

Another strategy to broach the stratum corneum is to use tiny arrays of microneedles either to allow drug diffusion directly from a drug-impregnated patch ("poke with patch") or to act as drug carriers through needles surface-coated with drug ("coat and poke").[26] Although these needles enter the epidermis where nerves are present, they are reported to be painless by human subjects. This technology has been studied in the context of the transdermal delivery of insulin and desmopressin.[27,28]

Iontophoresis and electroporation use an electric field to enhance the skin penetration of polar drug molecules.[1,29] These technologies have been investigated for transdermal delivery of peptides such as insulin, calcitonin, vasopressin, and octreotide, and nonpeptide drugs such as opioids, nonsteroidal antiinflammatory agents, and antiemetics.[29] Although they may seem cumbersome and potentially painful, iontophoretic devices are available commercially that are compact, battery-operated, and well tolerated by human patients (e.g., Iontopatch 80, Sammons Preston Rolyan, Bolingbrook, IL). Such an approach has not been evaluated in veterinary patients, although human PTH (used for treatment of osteoporosis) has been delivered successfully to dogs with the use of iontophoresis under experimental conditions.[30]

Commercially Available Transdermal Drugs Used in Cats

Nitroglycerin ointment has been used transdermally for decades in veterinary patients to reduce preload in acute heart failure.[31,32] Nitroglycerin is a relatively small molecule (227 molecular weight) that causes local venodilation and increases local blood flow, which may contribute to its transdermal absorption. Interestingly, transdermal nitroglycerin also has been used in human beings to treat local neuropathic pain after thoracotomy,[33] an application that has not been explored in veterinary patients.

The fentanyl patch, developed for use in human beings (Duragesic, Janssen Pharmaceutica, Titusville, NJ) has been well studied in veterinary patients and has been shown to be effective in the management of postoperative pain associated with ovariohysterectomy, onychectomy, and orthopedic procedures in dogs and cats.[34-38] Transdermal fentanyl causes less

sedation and hypothermia than injectable narcotics[35,36] and can provide analgesic plasma concentrations for 3 to 5 days in cats and 1 to 3 days in dogs.[39,40] Patches are available in 25, 50, 75, and 100 µg/h sizes, and are applied, at a dosage of 3 to 5 µg/kg/h, to shaved skin that is cleaned with warm water and alcohol, and dried thoroughly before application. Exposure to the skin of only half of a 25 µg/h patch (achieved by removing only half of the liner, without cutting the patch) provides effective postoperative analgesia in cats and has been advocated for cats smaller than 4 kg.[41]

The use of fentanyl patches has several drawbacks, including variable absorption among individuals[39,42] and the need for application 12 hours (cats) to 24 hours (dogs) before surgery.[39,40] In addition, heating pads in contact with the patch can accelerate fentanyl absorption, and hypothermia under anesthesia (e.g., 35°C) can decrease absorption significantly,[43] both of which may alter clinical response.

Commercially available "spot-on" insecticides and acaricides are common in the veterinary market. Fipronil (in Frontline, Merial Ltd, Duluth, GA) and imidacloprid (Advantage, Bayer Animal Health, Shawnee Mission, KS) are topical agents that distribute to the hairs, stratum corneum, and sebaceous glands, but not to the systemic circulation.[43-45] Selamectin (Revolution, Pfizer Animal Health, Groton CT), which is an insecticide and acaricide, is formulated in dipropylene glycol ether and isopropanol and is absorbed systemically. Selamectin has a much higher transdermal bioavailability in cats (74 per cent) compared with dogs (4 per cent), possibly because of thinner skin in cats or ingestion by grooming.[46]

Custom Formulated Veterinary Transdermals: Absorption and Efficacy

Methimazole in PLO is the first custom transdermal drug formulation for which absorption and efficacy data have been obtained. In an initial case series, Hoffmann et al described decreases in serum thyroxine (T_4) in 13 cats treated with 2.5 to 10 mg of methimazole in PLO q12-24h.[47]Although methimazole in PLO is absorbed poorly in healthy cats after a single dose,[48] chronic dosing likely leads to improved absorption, because transdermal methimazole is efficacious in many cats with hyperthyroidism. In a randomized, prospective study in hyperthyroid cats, owners dosed their cats with methimazole orally (tablets) or transdermally (in PLO; 50 mg/ml) at 2.5 mg q12h.[49] Methimazole in PLO was applied to the unhaired portion of the cats' inner pinnae by owners wearing finger cots or exam gloves. The owners alternated ears with each dose and removed any remaining crusted material before the next dose. Fifty-six per cent of cats treated by the transdermal route were euthyroid at 2 weeks. Although this was significantly fewer cats than were controlled in response to oral administration (88 per cent of cats were euthyroid at 2 weeks), transdermal methimazole was associated with significantly less gastrointestinal upset (4 per cent) than oral methimazole (24 per cent). Whether transdermal administration for a longer period of time would have controlled the hyperthyroidism in more cats was not evaluated. However, the incidence of hepatopathy, facial excoriation, and blood dyscrasias was similar for both the transdermal and oral routes.[49] Some cats developed erythema at the transdermal dosing site, but it was not severe enough to require drug discontinuation in any case.[49] I have switched treatment successfully from oral to transdermal methimazole in several cats that developed GI upset from oral methimazole, without subsequent problems by the transdermal route.

Like methimazole, single-dose bioavailability studies have been reported in veterinary medicine for a handful of other drugs formulated in PLO for transdermal administration. Fluoxetine (15 per cent in PLO) was only 10 per cent bioavailable relative to oral fluoxetine but roughly comparable AUC (area under the curve) values for fluoxetine and its active metabolite, norfluoxetine, were obtained by dosing transdermal fluoxetine at 10 mg/kg (ten times the 1 mg/kg oral dose) in cats.[50] However, this formulation dosed at 10 mg/kg per day chronically caused significant irritation and could not be used for maintenance treatment.

Administration of fentanyl and morphine in PLO provided essentially undetectable serum concentrations after single transdermal doses of 0.88 mg/kg for transdermal fentanyl (almost 90 times the IV dose) and 2 mg/kg for transdermal morphine (almost seven times the IV dose).[51] Similarly, no significant absorption of dexamethasone occurred after a single transdermal dose in PLO (0.05 mg/kg),[52] and buspirone and amitriptyline also were absorbed poorly after single transdermal doses in cats.[53] Like fluoxetine, the bioavailability of a single dose of transdermal diltiazem in cats was about 10 per cent relative to oral administration.[54] For all of these drugs and for future studies, multiple-dose bioavailability and/or efficacy needs to be evaluated, because absorption may be enhanced with chronic dosing.

Considerations for the Use of Transdermal Drugs Without Absorption or Efficacy Data

Only relatively potent drugs are developed for transdermal administration in human beings, with a total daily dosage requirement generally less than 50 mg per day (for 70 kg person) and therapeutic plasma concentrations in the ng/ml range.[29] Existing patches generally are limited in size to 50 cm^2 (less than 3 inches square) for practical and cosmetic reasons, and the human stratum corneum limits transdermal delivery of drugs, even with chemical permeation enhancers, to about 1 mg per cm^2 of skin surface area. Further work is needed to determine the limits for maximal transdermal delivery over a given surface area in dogs and cats. However, this "50-mg constraint" is a consideration in the prescription of transdermal formulations of drugs with high total daily dosages in veterinary patients.

In making the decision to prescribe a transdermal formulation for an individual patient, clinicians should consider a checklist of suggested criteria (Table 18-2). No single rule is useful to extrapolate an oral dose to a transdermal dose in the absence of multiple dose bioavailability or efficacy data. Transdermal doses may need to be much higher if skin penetration is poor, could be the same as the oral dose for drugs for which transdermal and oral absorption are comparable, or may need to be much lower for individual drugs with extensive first pass hepatic or intestinal metabolism. Only drugs with a quantitative therapeutic endpoint (e.g., measurement of serum T_4 concentration to judge efficacy of methimazole) should be chosen, and dosage should be adjusted to effect. Because titration from a low starting dose may be necessary to avoid toxicity, the transdermal route is not recommended for empirical dosing of antimicrobials because dose titration could lead to microbial resistance. In addition, the dosage of most antimicrobials in cats

Table 18-2 | **Suggested Criteria for the Use of Transdermal Medications Without Absorption or Efficacy Data**

CRITERIA	EXAMPLES, COMMENTS
Other proven routes of administration are *not possible.*	Fractious cat, severe intestinal malabsorption
A quantitative endpoint can be measured.	Serum T_4 or blood glucose concentration, blood pressure, heart rate, plasma drug concentrations
The drug has a relatively large margin of safety.	Drugs with narrow margins of safety are inappropriate for empirical transdermal dosing (e.g., calcitriol)
A rationale exists for the dose.	For example, starting with the oral dose and titrating to quantitative endpoint (only acceptable for drugs with large margins of safety)
An immediate clinical response is not needed.	Empirical transdermal administration is not appropriate for conditions that require immediate efficacy (severe hypertension, bronchospasm, seizures, cardiac arrhythmias, hyperkalemia, pulmonary edema)
The client is informed that the appropriate dosage is not established for this route.	Applies to all transdermals for which relative bioavailability or efficacy are not established
The pharmacy can provide information on the constituents of the formulation.	Important if a local or systemic hypersensitivity reaction should develop
The pharmacy can provide stability information or a shelf-life for the formulation.	Information often lacking

exceeds the "50-mg constraint" for transdermal absorption established in human beings.

SUMMARY

The strategy of transdermal delivery of drugs offers many opportunities to the veterinary profession, including better client and patient compliance, the potential for prolonged duration of action, and individualization of dose for very small patients. The widespread availability of dozens of drugs in transdermal PLO gels from custom compounding pharmacies has leap-frogged ahead of the studies that are needed to answer the most basic questions about these formulations, such as, what is a safe and efficacious dose? New information on the use of ultrasound, electric current, and painless microneedles in human beings begs for more research on the application of these techniques to veterinary patients.

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Chapter 19

Pathogenesis and Management of Obesity

Margarethe Hoenig and Jacquie S. Rand

Obesity is an excessively high amount of body fat or adipose tissue in relation to lean body mass. The incidence of obesity is increasing at a rapid rate in human beings and in pets. It is now considered the most common nutritional disorder of cats and dogs in the United States. Obesity in cats concerns veterinarians because it increases the risk of other diseases, in particular, diabetes mellitus, dermatopathies, and lameness.[1]

Obesity occurs when energy intake exceeds energy output.[2] Because of the simplicity of this formula, its prevention would seem to be an easy task, especially in indoor cats whose environment can be controlled almost completely by their owners. However, veterinarians often find it difficult to implement measures that lead to weight loss in an overweight pet, which suggests that the problem is multifaceted and goes beyond mere physiology. Several theories, which include genetic, metabolic, and environmental causes, have been postulated to explain the recent rise in obesity.[3] Similar factors likely play a role in the development of complications of obesity such as diabetes mellitus. However, just as in human beings and other species, not all obese cats become diabetic and about one third of all obese cats do not show glucose intolerance[4] or insulin resistance, which suggests that protective factors exist.

Although many aspects of obesity are similar among species, numerous differences also exist. For example, obesity in people frequently is associated with dyslipidemia. Development of cardiovascular disease and hypertension has been attributed primarily to an increase in low density lipoprotein (LDL), the so-called "bad" cholesterol, and a decrease in high density lipoprotein (HDL), the so-called "good" cholesterol.[5] In comparison, cats have elevated HDL concentrations when they become obese,[6] probably because of lack of cholesteryl-ester-transfer protein (CETP), an enzyme involved in the transfer of cholesterol and lipids between different lipoproteins.[7,8] Interestingly, this enzyme recently has been targeted to treat dyslipidemia in people; that is, inhibition of CETP leads to increased HDL and decreased LDL concentrations.

DEFINITION OF OBESITY

Although obesity is now recognized to be a major health problem and is defined based on objective measurements in human medicine, this is not the case in veterinary medicine. Many veterinary medical records still do not list obesity as a problem. Well-defined, objective parameters to distinguish between a cat with normal weight, one that is overweight, and one that is grossly obese do not exist. The body scoring system developed by LaFlamme[9] was a great improvement in the ability to categorize changes in body mass in cats. However, it is a subjective assessment and can be difficult to use in cats, especially in those that have lost weight recently or that have long hair.

Objective ways to judge obesity in cats do exist. Some require specialized equipment, whereas others do not. Body mass index (BMI) is well known from human medicine, where it is used ubiquitously to assess adiposity. It can be calculated in cats according to the following formula:

$$\text{BMI} = \text{Body weight (kg)}/(\text{Body length [m]} \times \text{Height [m]})$$

where height is the distance from the point of the shoulder through the point of the elbow to the proximal boundary of the metacarpal pad, and length is the distance from the point of the shoulder to the tuber ischium.[10] Obesity also can be assessed by measuring the girth circumference immediately caudal to the last rib.[11] Both girth and BMI measurements do not need any specialized equipment. Highly sophisticated evaluations of adiposity include dual energy x-ray absorptiometry (DEXA) and magnetic resonance imaging. However, we have found that BMI and girth (Figure 19-1) correlated well with DEXA results and are excellent objective markers of adiposity that could be used by clinicians (unpublished data).

PATHOGENESIS

Changes in both insulin secretion and action play a primary role in the pathogenesis of obesity and diabetes mellitus.

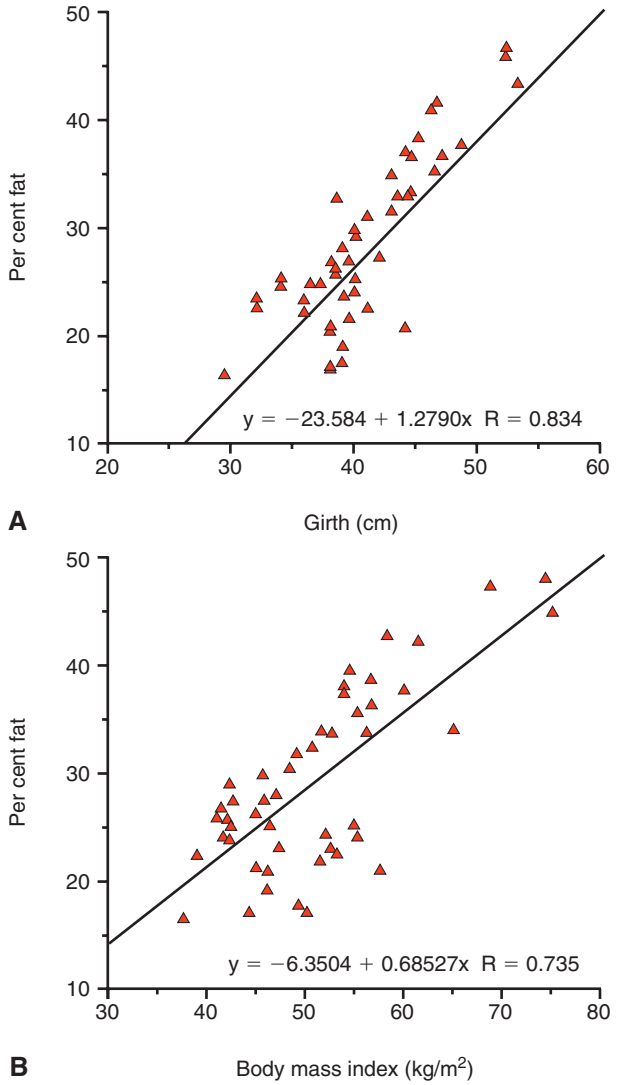

Figure 19-1. Scatter plot of **(A)** per cent fat (measured by DEXA) and girth (cm) and **(B)** per cent fat and body mass index (kg/m^2) in 46 cats with varying degrees of adiposity.

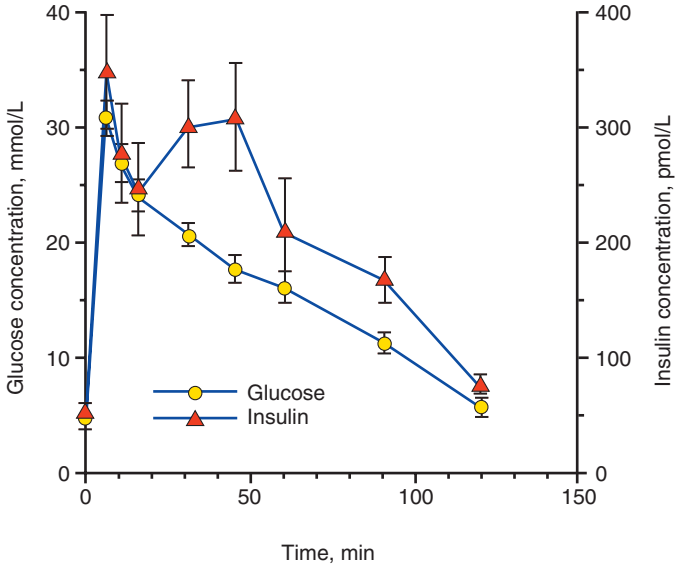

Figure 19-2. Insulin secretion and glucose disposal during an intravenous glucose tolerance test (1 g/kg body weight; 50 per cent glucose, w/v) in eight lean cats.

Insulin Secretion

Insulin secretion has been evaluated in cats primarily with the intravenous glucose tolerance test (IVGTT),[12-15] although this test measures insulin action and secretion. Glucose is the major stimulus for insulin secretion in cats as in many other species.[16] Other substances such as amino acids also cause insulin release but only in the presence of glucose. During an IVGTT, the response to an IV bolus of glucose is measured over a 2-hour time period. In healthy lean cats, glucose leads to a biphasic release of insulin, which is characterized by an acute or first phase and a second or maintenance phase (Figure 19-2). Serum glucose and insulin concentrations return to baseline concentrations at 2 hours.

When cats become obese, the secretion pattern seen in an IVGTT changes and is characterized by a decrease in the area under the curve (AUC) of the acute or first phase but an increase in AUC of the second or maintenance phase.[4] Other species have demonstrated that the rapid, acute phase is necessary for the inhibition of glucose output by the liver; therefore in obese animals with a diminished acute phase, hepatic glucose output rises.[17] The increase in the second phase likely is due to peripheral (tissue) factors that cause insulin resistance and a response to the increase in endogenous glucose concentrations.

Changes in insulin secretion on an IVGTT actually may precede obesity as well. In a group of lean cats from a varied genetic background housed identically and fed ad libitum, all cats became obese but only a proportion became glucose intolerant. Interestingly, those that became glucose intolerant had an increased second-phase insulin secretion even when still lean, which suggests that the action of insulin was decreased and that peripheral insulin resistance may precede a defect in insulin secretion.[11] Perhaps this group progresses later to overt diabetes; however, no proof of this exists at this time.

A highly specific marker of changes in insulin secretion and predictor for progression to diabetes mellitus in human beings is the insulin/proinsulin ratio.[18,19] Normally insulin is made as a precursor molecule, proinsulin, which is then processed; that is, part of the amino acid chain is cleaved, making the mature molecule, insulin. With increasing demand for insulin secretion in obese subjects, the cleavage of proinsulin to insulin becomes inefficient, more proinsulin is secreted, and the ratio decreases. However, because of the lack of a feline assay specific for proinsulin versus insulin, whether this phenomenon occurs in cats has not been examined.

Insulin Resistance

Obesity is characterized in many species by insulin resistance, which is defined as the inability of insulin to promote glucose uptake and to suppress hepatic insulin output.[21] Insulin resistance is present in obese cats as has been shown recently in experiments with use of the gold standard testing method, the euglycemic hyperinsulinemic clamp.[22] Obese cats showed an approximately 50 per cent decrease in insulin sensitivity compared with lean cats, possibly because, at least in part, of

changes in glucose transporters. In many tissues, including muscle and fat, insulin facilitates glucose entry by increasing translocation of glucose transporters to the cell membrane. GLUT4 is the major insulin-sensitive glucose transporter found in muscle and fat, whereas GLUT1 is insulin independent and found in most tissues throughout the body.[20] In muscle and fat from obese cats compared with lean cats, GLUT4 expression is decreased several-fold, whereas GLUT1 expression is unchanged.[23] These changes occurred early in the development of obesity when fasting glucose concentrations or glycosylated hemoglobin concentrations were not different between the two groups, which suggests that factors other than glucose are causing initial changes in insulin action.

Changes in fat metabolism may alter the actions of insulin. In human beings and other species, obesity leads to an increase in nonesterified fatty acids (NEFAs), which are thought to cause insulin resistance.[24] Obese cats similarly have elevated NEFA concentrations, with higher levels in obese males than females.[4] Myocellular lipid deposition also may lead to insulin resistance. In rodents,[25] human beings,[26] and cats,[11] the triglyceride content of muscle correlates negatively with whole body insulin sensitivity, and obese cats have an increase in muscle lipid content as measured by magnetic resonance imaging.[11] In lean subjects, fatty acids are oxidized in muscle; however, with obesity, oxidation decreases and reesterification increases. The result is lipid deposition, which is thought to interfere with glucose uptake and metabolism.

The response of obese cats to the thiazolidinedione drug darglitazone[27] supports the notion that lipid oxidation is abnormal and causes changes in glucose metabolism. Treatment of obese cats with darglitazone led to increased insulin sensitivity.[27] Part of the physiological action of this classification of drugs is related to their ability to bind to and activate the nuclear peroxisome proliferator activating receptor γ (PPAR γ). PPAR γ is expressed in several tissues[28] and is required for adipogenesis. On one hand, thiazolidinediones increase lipogenesis,[29] but through stimulation of expression of mitochondrial uncoupling proteins 2 and 3, they also increase fatty acid oxidation and enhance thermogenesis and energy dissipation.[30,31] As a result, intracellular lipid is redistributed from insulin-responsive organs such as muscle into peripheral adipocytes, thereby increasing insulin sensitivity.

Increased lipids are involved in decreasing glucose transport and in increasing hepatic glucose production. Initially, pancreatic β cells increase insulin secretion to compensate for two changes that occur in obesity: increased endogenous glucose production and decreased clearance. As a result, blood glucose concentrations remain in the normal range. However, with time, β-cell function declines and blood glucose concentrations increase, a phenomenon referred to as "exhaustion,"[32] which likely is due to a combination of changes in lipid and glucose metabolism (glucotoxicity and lipotoxicity), among others.[33]

A change in amylin secretion may contribute to the decline in β-cell function. Amylin is a protein co-secreted with insulin that serves as the precursor molecule for the type of amyloid that forms in the pancreatic islets of most diabetic cats. In dogs with insulinomas[35] and in cats treated with the sulfonylurea glipizide,[34] continued stimulation of insulin secretion leads to amyloid deposition, which suggests that any long-term stimulation of insulin secretion, such as obesity, potentially could cause islet amyloid formation. Although amylin and insulin secretion increased together in cats made insulin-resistant,[34] it is unclear what role amyloid plays in the pathogenesis of feline diabetes. Not all glucose-intolerant cats have pancreatic islet amyloid deposition, and the amount of amyloid deposited does not correlate highly with β-cell functional defects. Unfortunately, the ability to perform controlled studies to evaluate the relation between amyloid deposition and insulin secretion is limited, because it is too invasive to evaluate cat pancreata histopathologically at different stages of insulin resistance and during the progression to diabetes. In addition, true loss in islet mass resulting from amyloid is difficult to quantify because pancreatic weight usually is not recorded at necropsy. However, recent evidence in transgenic mice suggests that amylin can form toxic molecules, which lead to β-cell apoptosis, and β-cell loss correlated positively with increasing glucose concentrations.[36] Therefore amyloid deposition probably is not a cause of the initial defect in insulin secretion but may contribute to the progressive β-cell failure in the majority of glucose-intolerant cats.

Many other hormones and cytokines are thought to be involved in the development of obesity and diabetes. Of those, leptin and adiponectin recently have received attention and have been examined in obese cats.[37-39] Both are secreted from white adipose tissue, now considered an endocrine organ because it secretes cytokines and hormones, many of which influence glucose and lipid metabolism.[40] Leptin is the product of the "obesity gene" and modulates energy balance through central (satiety signal) and peripheral (energy expenditure) actions. The high leptin concentrations found in obesity are believed to be an indication of leptin resistance. Triglycerides recently have been implicated in the pathogenesis of leptin resistance, because they inhibit leptin transport into the brain, where it would act as a satiety signal.[41] Leptin concentrations are increased in obese cats and decrease with weight loss, and therefore can be considered a marker of adipose mass.[37]

Adiponectin expression and secretion are stimulated by PPAR γ, and serum concentrations are correlated positively with insulin sensitivity. Adiponectin suppresses glucose production and inhibits inflammatory pathways and therefore plays an important role in the protection from atherosclerosis in human beings. Serum adiponectin concentrations are decreased in obesity and type 2 diabetes.[42]

Much more must be learned about the role of adipose tissue as an endocrine, paracrine, or autocrine organ before any conclusions about the role of these factors in the pathogenesis of obesity and diabetes can be drawn. Many actions and interactions still must be elucidated.

PROGRESSION TO DIABETES

The incidence of diabetes in cats clearly has increased in the last two decades, likely because of the increase in risk factors in general and obesity in particular. However, as stated above, not all obese cats progress to becoming diabetic. Conversely, not all diabetic cats are obese at the time of diagnosis or ever have been. Not all diabetic cats have an increased amount of pancreatic amyloid deposition, and even cats with increased islet amyloid concentrations may have only transient diabetes.[43] Last, not all diabetic cats respond to the same treatment. Many factors therefore are likely involved in the pathogenesis and clinical presentation of this disease. Learning more about feline physiology will enable us to detect early changes that indicate pathology and intervene to prevent diabetes from developing.

MANAGEMENT OF FELINE OBESITY

Management of feline obesity involves decreasing body weight and addressing the side effects of obesity until an ideal body weight is achieved. For successful management of obesity, owners must be committed to the goal of having their cat achieve a healthy body weight. Owners need to understand and believe that prevention or appropriate management of obesity leads to a more active and healthier pet and a longer life. The evidence that obese cats have nearly three times the risk of death than cats of ideal weight helps to convince some owners.[44] The data in dogs showing that a body condition score of 7/9 reduced lifespan by 20 per cent, or 2 years, compared with dogs with a body condition score of 4/9, also are a powerful argument.[45] The reduction in lifespan was in dogs classified merely as overweight. The consequences of obesity or morbid obesity are likely to be more profound.

Making Weight Loss Happen: Increasing Physical Activity

One of the cornerstones of obesity management is that physical activity should be increased. Increasing physical activity in cats is not as easy as in dogs but is important in a weight management program. In a recent study, active play in cats for 10 minutes daily produced the same weight loss as calorie restriction.[46] In a weight loss study over 8 weeks, cats given environmental enrichments, such as additional food dishes, water bowls, and litter boxes, climbing towers, window perches, scratching posts, cat spas, and grooming supplies and toys, had significantly increased activity levels as measured by an activity monitor and had a trend toward greater weight loss compared with cats that did not have an enriched environment.[47]

Other strategies that may aid in increasing physical activity include feeding cats with devices that require physical activity to obtain food. For example, food can be hidden inside a treat ball, with exertion being required to get the ball to roll so that food is released. Placing the food at the top of stairs or on top of a climbing frame also can help increase movement. Because cats kept indoors are less energetic than cats with access to the outdoors and are at greater risk of developing diabetes mellitus, allowing cats outside for limited hours in daylight may help in achieving ideal body weight.[48] However, this should be balanced carefully by health risks such as car accidents and cat fights. Modular units are available commercially that allow outside access while protecting cats from these risks.

Making Weight Loss Happen: Calorie Restriction

The other cornerstone of managing obesity is to restrict caloric intake. Before a dietary weight loss program is formulated, obtaining an accurate dietary history is important, including treats, table food, and other sources of food, such as other pets' food. Identification of the person who feeds the cat is important, including children in the household and neighbors. This makes it more likely that observable success is obtained early in the program. Without an accurate dietary history, prediction of what initial caloric intake will achieve the goal of 1 to 2 per cent loss of body weight per week is impossible. Cats have variable energy requirements, and some obese cats have low energy requirements.[49] Therefore if the standard caloric intake for weight loss is simply recommended, many obese cats will not lose weight until caloric intake is further reduced. Indeed, some cats will not lose weight until caloric intake is reduced to 30 to 35 cal/kg/day or less!

Label information and information provided by the manufacturers are required to estimate a cat's current caloric intake. If not available at the first interview, owners should provide details of a cat's diet as soon as possible, if early success is to be achieved. An owner may need to keep a food diary for several days to identify clearly how much a cat eats.

For a weight loss program to be successful and safe, calories should be restricted to 80 per cent of current intake. However, if accurate assessment of a cat's current intake is not possible, feeding 60 to 70 per cent of postulated daily energy requirement (set at 60 kcal/kg ideal weight) is the best solution (i.e., 36 to 42 kcal/kg of ideal weight), but the owner must be warned that this level still may be too high to achieve weight loss for their cat. With repeated checks, eventually the caloric intake that provides effective weight loss is determined. However, it may take up to 2 months of visits for this to be become clear. Energy requirements often change with weight loss, and morbidly obese cats with very low energy requirements may have an increased energy demand once they achieve substantial weight loss and become more active. In other cats, weight loss plateaus after a time, presumably because of more efficient use of energy, and further energy restriction is required for continued weight loss.

To ensure success of a weight loss program, a cat's weight must be monitored frequently with initial visits every 2 weeks, increasing to every 3 to 4 weeks once evidence demonstrates that the owners are implementing the program correctly and weight loss of 1 to 2 per cent of body weight per week is occurring. Weigh-ins every 2 weeks provide confirmation of success to motivate owners, allow further adjustments in calories fed to maintain weight loss, and help solve implementation problems. Technicians can be trained to perform the weight checks, which can be time efficient for the practice and cost effective for the owners. (Some practices provide this service free if the client is purchasing food from the practice.) Providing owners with a graph of the body weight so that they can chart the progress often provides additional incentive. Identifying a target weight and interim milestones sets goals toward which owners can work. Because of the decrease in lifespan in dogs associated with a body condition score of 7/9 compared to 4/9, an ideal body condition would be a prudent goal. However, because even a 15 per cent reduction in body weight in obese human beings is associated with significantly improved health,[50] the same decrease can be used as a minimum goal for weight loss in obese cats.

The amount of food fed must be adjusted so that no more than 2.5 per cent of body weight is lost per week. For an 8-kg cat this translates to not more than 0.2 kg per week or 0.8 kg per month. Although most protocols aim for 2 per cent weight loss per week, cats typically achieve only 1 per cent weight loss when calculated over the duration of the program.[51] Owners must be warned not to reduce food intake even further because of the risk of hepatic lipidosis. Also, the more severe the calorie restriction, the smaller the proportion of weight lost from fat and the greater the proportion lost from muscle mass. When a weight loss of 1 per cent of body weight per week was achieved, 90 per cent of weight was lost from fat and less than 10 per cent from lean body tissue.

In general, feeding cats multiple small meals rather than one large meal seems better, which fits with the typical eating pattern of cats.[52,53] The greatest threat to successful weight loss is the impact of the human-animal bond on providing food. The act of feeding is associated with a positive emotional experience for many clients, and withholding food from an animal that is asking or begging for food can be extremely difficult for clients who have a close bond with their cat. All members of the family need to be informed about the weight loss program, including the use of treats. Neighbors who may feed the cat also should be educated.

Helpful practices include weighing out the calculated daily portion of food for a cat and marking the level on a measuring cup for clients to use at home. Clients should be instructed to fill the cup to that level once a day and ration out portions during the day. This allows clients to respond to a cat's request for more food without exceeding the daily calorie limits and avoids some of the emotional turmoil of denying a cat food. Some pieces of dry food also can be removed from the measured ration, to be used during the day as treats or rewards. If sources of snacks or treats other than the prescribed food are to be fed, their caloric content should be calculated and the amount of prescribed food reduced correspondingly. For example, owners can be instructed to remove five pieces of dry food for each piece of dried fish treat. To enhance success with the weight loss program, the veterinarian or technician can ascertain which types of treats owners typically give and then calculate the caloric equivalent in dry food pieces.

In multipet households, food restriction for just an overweight cat can be a particular challenge. Some strategies are to feed lean cat(s) on bench tops, if the obese cat is too heavy to jump, or to create a feeding box with an entry that only the lean cat(s) can fit through. Similarly, feeding cats in different rooms with the door tied open only enough for the thin cat to fit through is effective.

Diets that Assist Weight Loss or Minimize Weight Gain and the Side Effects of Obesity

Much of the data supporting beneficial dietary manipulations are based on small feline studies or data from human beings. An urgent need exists for larger, long-term studies on which to base recommendations in cats; however, these can be costly and take years to complete. For example, studies to examine the effect of low-carbohydrate diets on amyloid deposition could take more than 10 years. In general, cat foods are being altered based on the best available evidence and theory.

Several dietary manipulations are beneficial in minimizing the side effects of weight gain and in preventing further weight gain. Two of these involve altering the carbohydrate amount or glycemic load and changing the carbohydrate source.

The postprandial period in cats is prolonged. Glucose and insulin concentrations may be increased for 18 hours or more after a large meal is consumed, compared with 4 to 6 hours in dogs and human beings. Diets with 50 per cent of calories from carbohydrate resulted in mean and peak glucose concentrations that were 25 per cent and 32 per cent higher, respectively, than diets with 25 per cent of calories from carbohydrate.[54] Postprandial glucose concentrations in the high-carbohydrate diet were higher than the moderate-carbohydrate diet for 14 hours after a single meal (from 4 to 18 hours after eating), which puts a high demand on β cells to secrete insulin. Some feline low-calorie diets are designed for weight loss and some supermarket-brand feline maintenance dry foods have approximately 50 per cent of calories from carbohydrate.

Many obese cats are glucose intolerant and hyperinsulinemic. Because high insulin concentrations long term are postulated to promote β-cell burnout and lead to type 2 diabetes, diets with reduced carbohydrate load that help lower postprandial glucose and insulin concentrations would be advantageous.[55,56] Cats evolved as obligate carnivores, and feral cats typically eat diets high in fat and protein and low in carbohydrate. For example, a rat carcass has less than 5 per cent of calories derived from carbohydrate. Lowering insulin secretion, and therefore amylin secretion, also may help to protect pancreatic β cells from loss associated with amyloid deposition.

Because the human-animal relationship makes it difficult for owners not to feed a pet that is begging, diets that are associated with high satiety would be advantageous in facilitation of weight loss. Evidence in human beings suggests that diets that produce high postprandial insulin concentrations are associated with low satiety. More calories were consumed after meals with a high glycemic load and high postprandial insulin concentrations than meals with a lower glycemic load.[57] Anecdotal evidence also exists in some cats that low-carbohydrate, high-protein diets are associated with greater satiety. In addition, initial data suggest that lean mass (muscle) is maintained better during weight loss if a high-protein and therefore low-carbohydrate diet is used.[58] Diets that result in higher postprandial insulin concentrations are thought to facilitate fat deposition because of the anabolic action of insulin. A low-protein, high-carbohydrate diet decreased NEFA mobilization in cats compared with a high-protein, low-carbohydrate diet.[56] In summary, purported evidence against using a traditional high-carbohydrate, low-fat diet in cats for weight loss is that it promotes β-cell loss from apoptosis and amyloid deposition in susceptible cats; is associated with reduced satiety, higher calorie intake, and greater loss of muscle mass; and promotes fat deposition and maintenance of fat mass. However, minimal data exist in cats yet to support these hypotheses.

For cats that require a restricted protein diet because of renal failure and therefore are eating a high-carbohydrate diet, selection of a renal diet that has a carbohydrate with a low glycemic index would be advantageous. A diet with 30 per cent of calories from corn and sorghum produced lower postprandial glucose and insulin concentrations in cats than a diet with 30 per cent of calories from rice and led to consumption of fewer calories and lower weight gain in cats fed ad libitum.[59] Rice is the carbohydrate source used most commonly in feline diets.

Other dietary alterations or additives may be beneficial in induction of weight loss or reduction of the side effects of obesity. The type of fatty acid in the diet appears to influence insulin sensitivity. A recent study in cats showed that a diet high in omega-3 polyunsaturated fatty acids (3-PUFAs) decreased plasma insulin concentration and was associated with lower glycated hemoglobin concentrations than a diet high in saturated fatty acids.[11] Carnitine supplementation in obese cats during weight loss increased fatty acid oxidation, accelerated weight loss, preserved muscle mass, and decreased the severity of biochemical and histological changes indicative of hepatic lipidosis.[60] Based on these findings, it is likely beneficial in feline weight loss diets. If it is not included in the diet being fed, it can be administered orally (250 mg/cat q24h of pharmacological grade product), added to food, or formulated

as an aqueous suspension. Chromium is a transitional element regarded as an essential nutrient.[61] It is considered beneficial only if the diet is deficient in chromium, but most Western diets for human beings are shown to be chromium deficient.[62] Chromium increases insulin sensitivity in dogs, human beings, and other species.[63-66] In healthy cats fed diets fortified by chromium tripicolinate, blood glucose concentration decreased in small but significant amounts during a glucose tolerance test, compared with cats fed the nonsupplemented diets.[67] Therefore the addition of chromium may provide a small benefit when incorporated as chromium tripicolinate into the diet. Also, vitamin A may help to reduce weight gain and aid in weight loss. Cats supplemented with vitamin A resisted weight gain after consumption of a high-fat diet.[68] As do the thiazolidinediones as mentioned above, vitamin A increases expression of mitochondrial uncoupling proteins.

Traditionally, weight loss diets have been supplemented with fiber to improve satiety. High-fiber diets have the disadvantage of causing greater stool formation, and the beneficial effect of fiber in feline diets has not been demonstrated convincingly. One study in diabetic cats compared diets with 1 per cent or 12 per cent insoluble fiber (cellulose), and found that the high-fiber diet reduced preprandial and most postprandial blood glucose concentrations compared with the low-fiber diet.[69] However, in the low-fiber diet, corn starch, a highly absorbable carbohydrate, was used in place of the fiber, which led to a different glycemic load between the two diets. Increased fermentable fiber, such as beet pulp, has been shown to improve glucose metabolism and increase satiety in other species.[70,71] Intestinal bacteria ferment the fiber and release short-chain fatty acids. These stimulate release of glucagon-like peptide-1, which in turn decreases glucose concentrations and suppresses appetite. However, fermentable fiber also increases insulin secretion, and a benefit in obese cats has not been reported to date.

Selection of a Diet

Adequate nutrition must be maintained during calorie restriction, so it is vital to use a diet designed for weight loss in cats. The required concentrations of nutrients such as total protein, essential amino and fatty acids, minerals, and vitamins are increased in weight loss diets, so that deficiencies of these nutrients do not occur. Intake of protein and other essential nutrients may be inadequate when some maintenance diets are fed at the restricted amounts required to produce weight loss. Protein intake must not be restricted with calorie intake because more muscle mass will be lost.

The choice of diet must be based on the owner and cat preference. In general, canned food has a lower carbohydrate content than the equivalent dry food, although for some prescription diets this is not necessarily true. Anecdotal evidence suggests that some cats have greater satiety and consume fewer calories when fed canned foods. Except in cases of renal disease, ideal diets have approximately 50 per cent of calories from protein and less than 25 per cent of calories from carbohydrate. This can be calculated from the dry matter values for the macronutrient by multiplying the value by 3.5 for protein and carbohydrate, and 8.5 for fat, and then recalculating the percentage of each present. For example, a diet with dry matter composition of 50 per cent protein, 25 per cent carbohydrate, and 25 per cent fat, when recalculated based on calories, has 36.8 per cent protein, 18.4 per cent carbohydrate, and 44.6 per cent fat. Added carnitine seems to be advantageous.

Adequate palatability is essential. The cat must be eating regularly, because fasting increases the risk of developing hepatic lipidosis during weight loss. Owners should be sent home with samples of several foods to see what a cat will eat. A cat should be transitioned to a new diet over 1 week, by substituting 15 per cent of regular food with the new diet initially, and increasing the proportion daily. The influence of the human-animal relationship must be addressed for weight loss to be successful. If owner pleasure from feeding a cat can be maintained, situations in which denial of food are minimized, and treats or rewards are allowed, then a cat is more likely to achieve and maintain a healthy body weight.

Other medical strategies exist for improving insulin sensitivity and causing weight loss. Insulin sensitivity and lipid metabolism can be enhanced in obese cats using the insulin-sensitizing drug, darglitazone.[27] However, this requires daily oral medication and may be most useful in cats in which glucose intolerance has developed because β cells are unable to secrete sufficient insulin to overcome the insulin resistance. In addition, no data exist to show that darglitazone therapy would benefit obese cats long term. For many owners, dietary intervention to achieve weight loss is a simpler method of improving insulin sensitivity. Weight loss methods used in people such as surgical reduction of fat, liposuction, and appetite-altering drugs are not recommended currently. Exogenous thyroid hormone should be administered only in cases of proven hypothyroidism.

Once the desired body weight is reached, the amount fed can be increased by 10 per cent. The cat should be weighed every 2 to 4 weeks to ensure weight gain is not occurring. Food intake can be increased a further 10 per cent if weight loss persists, but the cat should be monitored carefully to prevent weight gain. Adjusting calories to maintain the ideal weight is important. In one study, cats fed ad libitum after a weight loss program regained weight rapidly in a shorter time than it took to lose the weight, and the more severe the energy restriction that caused the weight loss, the faster the weight was regained.[72]

In conclusion, client education and coaching are paramount to the success of a weight loss program. Failures occur typically when the effect of the human-animal relationship overrides an owner's commitment to achieve weight loss, or when the calories calculated are in excess of a cat's needs, and the cat does not have noticeable weight loss. In these situations, clients become discouraged and do not return for repeat visits, and the opportunity for intervention is lost.

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Chapter 20

Options for Monitoring Diabetic Cats

Linda M. Fleeman and Jacquie S. Rand

The key to successful long-term management of diabetes in cats is individualization of advice to suit cat and owner. A relationship based on trust and cooperation between veterinarian and client leads invariably to the most satisfactory outcome. Success requires knowledge of the options for monitoring diabetic cats, selection and adaptation of appropriate techniques for each individual case, and provision of ongoing support and guidance for owners. The ongoing treatment of a diabetic cat can be one of the more rewarding experiences of feline practice, and many diabetic cats and their owners come to occupy a special place within the clinic environment. This chapter provides a comprehensive overview of the current options for monitoring diabetes in cats and guidelines for application of the techniques to clinical cases.

UNDERSTANDING THE PATHOPHYSIOLOGY OF FELINE DIABETES

Understanding the pathophysiology of feline diabetes is important for interpretation of response to therapy. The majority of affected cats have type 2 diabetes mellitus, characterized by a combination of inadequate insulin secretion and impaired insulin action (insulin resistance). A small percentage of diabetic cats have other specific types of diabetes resulting from pancreatic β-cell destruction because of pancreatitis or pancreatic adenocarcinoma, or have marked insulin resistance such as occurs with growth hormone excess. In cats with type 2 diabetes and other specific types of diabetes associated with marked insulin resistance, the most successful outcome of therapy is diabetic remission, and this requires that both insulin deficiency and insulin resistance be managed. Remission is not possible if diabetes is due to β-cell destruction. Many factors contribute to insulin resistance in cats including genotype, obesity, physical inactivity, administration of certain drugs (e.g., glucocorticoids), concurrent illness, gender, diet, and degree of hyperglycemia,[1] and these all influence disease progression and response to treatment.

The role of hyperglycemia has particular relevance for clinicians who monitor the response of diabetic cats to therapy. Chronic hyperglycemia causes insulin resistance in peripheral tissues and suppresses insulin secretion markedly from β cells, an effect termed *glucose toxicity*. In cats, suppression of insulin secretion occurs within 3 to 7 days of persistent hyperglycemia, and the severity of suppression is related to the level of hyperglycemia.[2,3] Initially, the suppression of β-cell function is reversible, but if marked hyperglycemia persists, β cells may be lost permanently.[3] Effective control of hyperglycemia in cats is important to minimize glucose toxicity, preserve β-cell function, and allow diabetic remission. In studies of healthy cats with glucose toxicity, effective control of hyperglycemia for just 1 to 2 weeks allowed β-cell function to recover.[3] This is consistent with observations in newly diagnosed diabetic cats treated with the long-acting insulin glargine, in which five of six diabetic cats achieved remission within 4 weeks of beginning insulin treatment.[4] However, elimination of glucose toxicity results in cats becoming more sensitive to insulin and a risk of insulin-induced hypoglycemia.

Clinicians also require knowledge of the complex interactions involved in glucose homeostasis. The major physiological mechanism for prevention of hyperglycemia is insulin secretion. In diabetic cats, this mechanism fails, and therapy with exogenous insulin usually is required to control hyperglycemia. Determination of an appropriate insulin dose to control hyperglycemia without inducing iatrogenic hypoglycemia remains the single greatest challenge when treating diabetic cats. Several physiological counter-regulatory mechanisms exist to prevent hypoglycemia. The acute response is mediated by glucagon and catecholamines such as epinephrine.

If the acute response is inadequate, long-term augmentation of the initial counter-regulatory response may be maintained by cortisol and growth hormone secretion. The overall effect of these counter-regulatory mechanisms is to promote hepatic gluconeogenesis and reduce the sensitivity of peripheral tissues to insulin, which results in a rapid increase of blood glucose concentration that may be sustained for several days. Indeed, the counter-regulatory response of diabetic cats to hypoglycemia induced by overdose with exogenous insulin (the Somogyi phenomenon) may occur so rapidly and persist for long enough that it may be difficult to differentiate from persistent hyperglycemia associated with an inadequate insulin dose.[5] Paradoxically, this results in a situation in which diabetic cats overdosed with insulin may present with clinical signs identical to those of diabetic cats that are underdosed.

OPTIONS FOR MONITORING HOSPITALIZED DIABETIC CATS

Diabetes mellitus in cats is associated classically with four clinical signs: polydipsia, polyuria, polyphagia, and weight loss.[6] However, any of these signs may be absent in individual animals. A variety of other clinical findings have been reported in newly diagnosed diabetic cats including lethargy, unkempt coat, anorexia or poor appetite, thin body condition, obesity, weakness, and dehydration.[6] These concomitant abnormalities may be associated with concurrent diseases or with development of ketoacidosis. A practical approach is to categorize newly diagnosed diabetic cats as either "well" or "sick" based on their appetite and demeanor. Cats that are eating well with minimal lethargy at the time of diagnosis are considered "well," whereas those with poor appetite, dehydration, and depression should be considered "sick." The latter require more intensive management aimed at correcting complicating factors and improving hydration, appetite, and demeanor before institution of a long-term therapeutic regimen for control of the diabetes. Ultimately, the goal is to commence long-term diabetic treatment in a cat that is "well."

Basic Monitoring of Hospitalized Diabetic Cats

Hospitalized diabetic cats should have routine daily quantification of water intake, frequency of urination, and body weight. Appetite and type and amount of food eaten also should be recorded. This simple and inexpensive monitoring allows collection of baseline clinical data in newly diagnosed diabetic cats, and a comparison to similar measurements at subsequent visits indicates response to therapy. Daily water intake correlates with the magnitude of hyperglycemia.[7,8] If blood glucose measurement is not scheduled, the presence or absence of glucosuria should be monitored daily in all hospitalized diabetic cats that are not polydipsic (i.e., water intake 10 mL/kg/24h or less when eating canned food, and 60 mL/kg/24h or less with dry food). Aglucosuria occurs when the blood glucose concentration remains below the renal threshold for the period of bladder filling and may alert clinicians to the possibility of diabetic remission or risk of hypoglycemia in a patient. In newly diagnosed or poorly controlled diabetic cats, a potentially useful tactic is to monitor the presence of urine ketones as an indicator of ketosis. Urine dipsticks designed to measure ketones also may be used to detect the presence or absence of ketones in plasma hematocrit samples of diabetic cats.[9]

Choosing a Point-of-Care Blood Glucose Analyzer

A wide range of portable blood glucose meters are available, and most are sufficiently accurate and precise to be useful for monitoring blood glucose concentrations in diabetic cats. The clinical value of various point-of-care blood glucose analyzers for use in cats has been evaluated[10-12]; however, manufacturers of these meters upgrade the models regularly and change their names, which sometimes may make it difficult to apply published data to the glucose meters currently available.

The performance of any individual meter used in-clinic or by an owner should be evaluated by comparison of results with those obtained using a laboratory reference method. Generally, meters are designed to be most accurate when measuring blood glucose concentrations in the normal range and are less accurate in the very low and very high ranges. Most meters also are designed to give lower results than the laboratory reference method to avoid erroneously missing hypoglycemia. For comparison of results obtained using a point-of-care blood glucose analyzer with results using a laboratory reference method, the clinical significance of any disparity should be evaluated. Clinically, it is crucial that a glucose meter can distinguish between hypoglycemia, euglycemia, and hyperglycemia accurately. The level of clinical risk of any meter errors must be categorized according to the effect on treatment decisions: (1) no treatment change or benign treatment; (2) treatment to lower blood glucose when already at acceptable concentrations; (3) dangerous failure to detect and treat; and (4) erroneous treatment that is contradictory to that actually required.[13] Therefore a meter that gives accurate and precise results in the range up to 180 mg/dL (10 mmol/L) and less accurate results in the 400 to 600 mg/dL (22 to 33 mmol/L) range would be considered clinically reliable.

Monitoring Blood Glucose Concentration in Hospitalized Diabetic Cats

Blood glucose concentration monitoring often is required in hospitalized diabetic cats, but in some cats, the results obtained may not accurately reflect blood glucose concentrations present when a cat is at home. Blood glucose may be higher or lower in cats while in the hospital. Stress hyperglycemia can occur within 1 to 2 minutes after struggling against physical restraint and is associated with an acute increase in plasma lactate concentration.[14] Therefore blood glucose measurement from a cat that struggled before or during sample collection can be expected to be higher than if the cat had not struggled. Consequently, great care must be taken to ensure that minimal physical restraint is used when obtaining samples for blood glucose measurement in cats and that struggling is not induced.

Even in cases of no struggling, clinicians must remain wary that blood glucose concentration results obtained from hospitalized cats may be higher than if the animal were not in hospital. This is because other factors that may be involved in the etiology of hospital-induced hyperglycemia (e.g., the role played by counter-regulatory hormones such as glucagon and cortisol in sustaining hyperglycemia) have not yet been elucidated fully. Conversely, because dietary carbohydrate has a marked effect on blood glucose in many diabetic cats from 4

to 20 or more hours after eating, blood glucose concentration may be lower when measured in hospital than at home, likely because of reduced food intake in hospital. This may be exacerbated by a change to a diet with lower carbohydrate content when in hospital. For all these reasons, accurate assessment during hospitalization requires that a patient maintains as normal a routine as possible, including the amount and type of food consumed.

Venous blood can be obtained by direct venipuncture, from an indwelling peripheral or central intravenous catheter, or by lancing the marginal vein of the lateral pinna. Application of topical local anesthetic cream to a site before venipuncture and use of a very small gauge needle improve patient comfort and cause minimal damage to the vein. Blood collection from indwelling peripheral and central intravenous catheters is tolerated well by cats and typically is associated with the least patient handling. Anesthesia, sedation, and/or physical restraint of a cat usually are required for catheter placement. Indwelling intravenous catheters in diabetic cats should be flushed with heparinized saline (5 to 20 U/mL) after blood collection[15,16] to protect against thrombus formation and catheter occlusion.

Small samples of venous blood can be obtained readily from the marginal vein of the lateral pinna of cats by first warming the area with a damp cloth, then applying petroleum jelly to the area and nicking the vein with an automatic lancing device.[5,16] A folded gauze swab is held against the medial pinna to provide support as the device is triggered. The petroleum jelly causes the blood drop to bead on the surface and prevents spreading of the sample into the surrounding fur. Occasionally, gentle massage around the nick site is required to increase droplet size. The technique can be performed with minimal physical restraint of a cat and often is well tolerated. Because the blood volume obtained with the latter technique is small, a glucose meter should be used that can operate with sample sizes less than 5 µL, such as the Glucometer Elite XL (Bayer Diagnostics, Bayer Corp, Elkhart, IN).

Measurement of capillary blood glucose concentration in diabetic cats is an alternative to the techniques using venous blood. Similar to the marginal pinnal vein method, the major advantage of capillary blood glucose measurement in hospitalized cats is that it can be performed reliably in patients with difficult venous access. Both techniques require some practice before they can be performed proficiently. However, once mastered, they are reliable and useful options for monitoring glycemia. For cats that tolerate the procedure, samples can be obtained with minimal physical restraint.

The medial aspect of the pinna is the only site from which capillary blood samples can be obtained in cats.[17] A vacuum-lancing device (Microlet Vaculance, Bayer Diagnostics, Bayer Corp, Elkhart, IN) is placed on the medial pinna so that the end cap is tight against the skin and forms a seal. A folded gauze swab is held against the lateral pinna to provide support as the device is triggered and the skin lanced. As the piston is released slowly, a vacuum forms within the end cup, which causes the skin surface to bulge and the blood drop to enlarge. Digital pressure against the folded swab must not be excessive because this may occlude blood flow to the site and prevent enlargement of the blood drop. Again, a glucose meter that can operate with sample sizes less than 5 µL should be used. Bilateral aural hematoma has been reported in one cat after repeated attempts at capillary blood collection.[18]

Monitoring Glycemic Response to the Initial Insulin Dose

Subcutaneous insulin therapy in diabetic cats should be initiated at a dose rate of 0.25 to 0.5 unit/kg (rounded down to the nearest whole unit) administered every 12 hours regardless of the type of insulin used.[19] For overweight or thin diabetic cats, the ideal body weight should be estimated and used for dosage calculation. This is particularly important for obese cats, because the risk of insulin overdose appears to be greater for this population.[20] The lower end of the dose range is most appropriate for cats with mild hyperglycemia (blood glucose concentration less than 360 mg/dL [20 mmol/L]).

Monitoring blood glucose concentrations after the first insulin dose is crucial to ensure that minimal risk of insulin-induced hypoglycemia occurs when a cat is discharged to its owner's care. Many cats do not have substantial glucose-lowering effect after the first injection; however, a few cats respond very well and have a considerably lower glucose concentration when the second insulin dose is due. For intermediate-acting insulin preparations, such as lente or NPH (isophane), blood glucose measurements should be obtained every 2 hours throughout the dosing interval if no nadir (lowest blood glucose concentration) exists or until blood glucose concentration is obviously increasing after a clear nadir, which usually occurs 2 to 6 hours after insulin administration. Blood glucose concentration also should be measured just before the second insulin injection. If the blood glucose concentration remains above 180 mg/dL (10 mmol/L) after the first injection of insulin, it is likely to be safe to send the cat home on this dose. If a blood glucose concentration nadir less than 180 mg/dL (10 mmol/L) is obtained after the first dose of insulin, the dose should be reduced by 1 unit/cat.

A different protocol is required for monitoring the blood glucose response of diabetic cats after the initial dose of longer-acting insulin preparations, such as glargine and protamine zinc insulin (PZI). Even with long-acting insulin, therapy should be initiated twice daily. However, as the average duration of insulin action exceeds 12 hours, this may result in a carryover effect of the previous insulin injection after administration of the next dose, and several days of therapy may be required before a complete glucose-lowering effect occurs. Therefore cats should be hospitalized for 2 to 3 days and serial blood glucose concentrations measured every 4 hours for 12 hours on each day beginning immediately before the insulin injection is given. Assessment of the blood glucose concentration when the insulin injection is due is important, as is the nadir blood glucose concentration each day. For PZI, the dose should be decreased by 1 unit/cat if a nadir less than 180 mg/dL (10 mmol/L) occurs. Because risk of hypoglycemia seems to be less with glargine therapy, no requirement exists to decrease the insulin dose unless the blood glucose concentration falls below 70 mg/dL (3.9 mmol/L).

The goal when monitoring the blood glucose response before discharge is to ensure minimal risk of insulin-induced hypoglycemia when a cat is at home. Too high an insulin dose must not be used from the outset, because insulin sensitivity will improve once chronic hyperglycemia and associated glucose toxicity resolve, which results in greater risk of hypoglycemia after several weeks of therapy. In addition, too high a dose of an intermediate-acting insulin can result in rebound

hyperglycemia and transient insulin resistance after hypoglycemia, making it difficult to achieve good glycemic control subsequently. If the initial response to insulin appears inadequate, an immediate increase of the dose is not necessary. Instead, the cat preferably is allowed to first equilibrate on the starting dose for 2 weeks. Clinical improvement, with reduction in polyuria/polydipsia and weight loss, occurs typically before good glycemic control occurs. Erring on the side of caution is always safest when prescribing the initial dose of insulin for a diabetic cat. If any doubt exists, to decrease the dose is preferable rather than risk the life-threatening possibility of hypoglycemia.

OPTIONS FOR MONITORING DIABETIC CATS AT HOME

Goals of Long-Term Management of Diabetes in Cats

The principal goals of treating diabetes in cats are to (1) achieve diabetic remission, if possible, (2) control all clinical signs while avoiding treatment-induced hypoglycemia, and (3) prevent diabetic ketoacidosis. Treatment aimed at maintaining blood glucose concentrations below 270 mg/dL (15 mmol/L) is more likely to resolve and prevent sequelae such as neuropathy, and lead to remission by facilitating the recovery of the pancreatic β cells from glucose toxicity.

Establishing a Practical Routine for the Cat's Owner

Many owners of diabetic cats welcome the opportunity to monitor their pet's response to therapy, although compliance can vary. Compliance is improved markedly if close rapport exists between owners and clinicians managing the case and with appropriate individualization of a cat's therapeutic and monitoring regimen. The veterinary clinician must invest time to educate owners about feline diabetes and its management and to provide support and guidance while they become accustomed to treatment and monitoring procedures and establish a practical routine. In diabetes management in human beings, professional diabetes educators take on much of this role and interpret and help to implement the medical advice for diabetic patients. Evidence demonstrates that patients who consult a diabetes educator regularly have significantly improved glycemic control and clinical outcomes, compared with those that deal only with their physician.[21-23]

The important role of education and support for owners in management of a diabetic cat cannot be overemphasized. Without guidance, a resourceful owner can readily discover and acquire the means to measure their cat's blood glucose concentration at home, yet few have sufficient knowledge of the complex interactions involved in glucose homeostasis in diabetic cats to fully interpret the results. Without guidance, owners may attempt to apply information about the protocols used to manage human diabetes to the management of their diabetic cat. This may lead to adjustment of insulin dose based on single blood glucose measurements, which is an ineffective protocol that often results in poor glycemic control for the cat and frustration for the owner.

Monitoring the Owner's Treatment Regimen

Some of the most common problems resulting in poor control of diabetic cats are incorrect measurement of the insulin dose, administration errors, and inappropriate insulin dose and frequency of administration. The minimum volume of a 100 U/mL insulin preparation that can be withdrawn repeatedly and reliably into a U-100 syringe is 2 units,[24] whereas the minimum accurate dose of 40 U/mL insulin preparations is approximately 1 unit. Doses of this order are prescribed commonly for diabetic cats and can be difficult for their owners to manage, particularly if they have poor vision or arthritic hands. Although most insulin preparations, except glargine, can be diluted with normal saline or insulin diluent, this generally is not recommended because it may shorten the duration of insulin action, and adequate mixing of insulin with diluent is difficult in an insulin syringe, which results in dosing errors.[25,26] Dosing errors are reduced if specific syringes are provided with each bottle of insulin. For all insulin preparations, 0.3-mL U-100 syringes usually are most appropriate as they are easiest to use to measure small amounts of insulin. However, if using U-40 insulin with U-100 syringes, owners must understand that each "unit" on the syringe actually equals 0.4 U of insulin. If making this conversion is too difficult for an owner, U-40 syringes should be used with U-40 insulin. Owners should be advised strongly against substitution of syringes, because overdosing or underdosing can occur inadvertently because the gradations on different syringes often represent different volumes. For example, the incremental gradations on a 1-mL 100-U syringe often represent twice the volume of those on a 0.5-mL 100-U syringe.

The insulin dosing technique of all owners of diabetic cats should be monitored carefully during the first 1 to 2 weeks of treatment at home and whenever a cat is re-evaluated. Practitioners must watch owners administer the insulin dose, and home visits may be required in some cases. Insulin dose measurement and injection technique should be checked. Expired insulin, inactive insulin (e.g., left in a car in summer), poor mixing of suspensions, failure of administration (e.g., injecting through the skin pinch onto the hair-coat), and the presence of air bubbles in the syringe causing administration of too low a dose all typically occur regularly during long-term management of diabetic cats.

The importance of avoiding an insulin overdose must be emphasized. If some insulin is spilt during injection, the owner should never give more at that time, even if it appears that the cat has received no insulin. If an owner is ever uncertain, the safest option is to withhold the injection, because the consequences of missing a single insulin dose are negligible. Every person in a diabetic cat's household must be aware of the clinical signs of hypoglycemia, which include lethargy, dilated pupils, trembling, ataxia, mental dullness, altered mentation, seizures, and coma. If signs of hypoglycemia develop, syrup containing a high glucose concentration should be administered orally. The syrup should be rubbed directly onto the oral mucosa if a cat has been seizuring or is comatose. Suitable syrups are marketed for use by human diabetics and should be kept in reserve by all owners of diabetic cats. Appetite often is not stimulated in diabetic cats during hypoglycemia, and an adequate increase in blood glucose concentration cannot be relied upon if a cat does eat.[27] Owners should be instructed to contact their veterinarian immediately if hypoglycemia

occurs. Insulin dosing should be discontinued until hyperglycemia returns, at which point a dosage reduction should be implemented.

Monitoring the Cat's Clinical Signs

Continuous monitoring of clinical signs is required for all diabetic cats, and all owners should keep a daily record of their pet's general demeanor, its appetite, and the amount of water consumed, and a weekly log of the ability of the cat to jump and its body weight. This provides the historical information that is essential for interpretation of results of glycemic measurement, regardless of which other options are chosen for monitoring diabetic control. Hyperglycemia occurs for many reasons including administration of an insufficient dose of insulin, rebound subsequent to hypoglycemia caused by an overdose, inadequate duration of insulin action for the dosing frequency, poor absorption of insulin, or presence of stress or concurrent illness, especially pancreatitis. To differentiate between these scenarios may be very difficult, particularly between cases of insulin underdose and overdose. Review of a cat's clinical signs over the previous weeks and months allows results of current blood glucose monitoring to be related to the overall response to therapy. One of the best indicators of insulin overdose in cats is identification of periods of good diabetic control or episodes compatible with hypoglycemia that precede signs of hyperglycemia.

General Demeanor, Recorded Daily

Every time owners interact with their cat, they tend to notice its general demeanor, yet it may be difficult for them to recall any changes accurately a few days afterward. Daily recording overcomes this problem and owners should be encouraged to note all their observations, particularly any lethargy or dullness.

Appetite, Recorded Daily

Daily records of a diabetic cat's appetite and the type and amount of food fed provide valuable information for clinicians monitoring the response to therapy. Changes in appetite should be related to any changes in body weight or condition. An increase in appetite in a cat that is losing weight may indicate poor diabetic control or concurrent disease such as hyperthyroidism. On the other hand, a decrease in appetite in a cat that is clinically well and has stable or increasing body weight may indicate further improvement in glycemic control and overfeeding. If an inappetent diabetic cat is unwell or losing weight, however, ketoacidosis or concurrent disease is likely to be present.

Amount of Water Consumed Over 24 Hours, Recorded Daily

Total daily water intake in cats can be calculated by adding the amount of water consumed and amount of water in the food eaten, but this is unnecessary. Although both thirst and appetite are influenced by hyperglycemia in cats, thirst apparently is a better indicator of the magnitude of hyperglycemia. In diabetic cats, the amount of water consumed over 24 hours has a significantly higher accuracy than total water intake for predicting level of glycemic control[8] and is better correlated with both mean blood glucose concentration and plasma fructosamine concentration in cats, providing a simple, accurate, and cost-effective indicator of diabetic control.[7] Healthy, non-diabetic cats drink 10 mL/kg/24h or less and 60 mL/kg/24h or less when eating canned food and dry food, respectively. Diabetic cats with exemplary glycemic control drink similar amounts. However, this level of control is difficult to achieve when intermediate-acting insulin preparations are administered twice daily, because minimal exogenous insulin activity occurs for periods of approximately 4 hours twice daily.[28]

Owners should be strongly encouraged to measure and record the amount of water consumed over 24 hours each day, or at least several times a week. The protocol usually has to be individualized to suit both the owner and cat. Common problems encountered by owners attempting to comply with this advice include more than one animal sharing the same water bowl, a cat drinking from places other than the water bowl, and lack of suitable equipment to measure water volume accurately. These problems sometimes can be solved easily. In other cases, compromises such as recording the amount of water consumed by all pets in the household or obtaining the measurement over a shorter period allows reasonable assessment of glycemic control. Some owners find it simpler to measure 24-hour urine output by weighing the litter box after removal of the feces, then subtracting the weight of the clean tray. Others prefer to log the number and size of urine clumps in clumping cat litter.

Ability of a Cat to Jump, Recorded Weekly

The ability of a cat to jump onto furniture or the owner's lap is the simplest and most effective indicator of activity level and neuromuscular function. Loss of the ability to jump may occur with hypoglycemia, diabetic neuropathy, hypokalemia, obesity, and many disease processes unassociated with diabetes. For cats that cannot jump, owners should monitor activity levels and hind limb function by recording the ability of a cat to perform less challenging activities, such as playing or stepping in and out of the litter box.

Body Weight, Recorded Weekly

Records of body weight are invaluable when monitoring diabetic cats. Unexpected weight loss always should be investigated promptly. Conversely, care is required to prevent and manage obesity because it contributes to insulin resistance. If regular reassessment of a cat is performed at a veterinary hospital, recording the body weight and condition at each visit is important. If a cat is to be monitored for long periods at home, the owners should be encouraged to acquire suitable scales and log weekly body weight measurements. Scales designed to weigh adult persons generally are not sufficiently sensitive for this purpose, and those intended for human infants are more appropriate.

Monitoring the Presence or Absence of Urine Glucose at Home

As for hospitalized cats, the presence or absence of glucosuria ideally should be monitored daily at home in all diabetic cats that are not polydipsic (water intake less than 70 mL/kg/day). This is very important because aglucosuria may indicate diabetic remission or risk of hypoglycemia. Because owners may

have difficulty assessing the amount of water consumed by their cats accurately and may require practice before becoming proficient at measuring urine glucose, a prudent approach is to recommend continuous weekly monitoring of urine glucose at home for all diabetic cats. However, owners must be cautioned against interpreting the magnitude of glucosuria seen on the dipstick as an indicator of their cat's level of diabetic control.

With encouragement and guidance, most owners can learn to monitor their diabetic cat's urine for the presence or absence of glucose. Litter glucose detectors that change color in proportion to the urine glucose concentration (e.g., Glucotest Feline Urinary Glucose Detection System, Nestlé Purina, St. Louis, MO) are a simple and reliable method. Alternatively, poorly absorbent litter material such as shredded paper allows collection of urine for dipstick measurement. Adding water to samples of regular cat litter that have been soaked with a cat's urine and then straining through a cloth also enables detection of glucose using a dipstick.[29] Alternatively, cats usually can be trained to accept direct application of a dipstick to the urine stream during micturition, and this is often the most practical method for cats that do not use a litter box.

Serial Blood Glucose Concentration Curves Obtained by Owners of Diabetic Cats at Home

Some owners are interested in measurement of blood glucose concentration of their diabetic cats at home. Single, sporadic measurements provide little useful clinical information for monitoring glycemic control, and serial blood glucose concentration curves that follow the same protocol as those obtained in hospital are required. As with blood glucose curves obtained in hospital, results must be related to a cat's clinical signs, and interpretation requires an understanding of the complex interactions involved in glucose homeostasis in diabetic cats.[5,19] Home-generated serial blood glucose curves are as reliable as hospital-generated curves but also have many of the same limitations. Considerable day-to-day variability in blood glucose measurements occurs in people with diabetes[30,31] and diabetic dogs,[32] and is likely also in diabetic cats. The major advantages of home-monitoring of blood glucose concentration are that measurements can be obtained easily at any time and can be repeated if equivocal results are obtained, the cost is minimal compared with a veterinary visit, and the effects of hospitalization on appetite and stress hyperglycemia are avoided.[33] However, micromanagement with frequent adjustment of insulin dose must be avoided and owners who choose this method of monitoring often need to be advised against overzealous blood glucose measurement and interpretation of the results themselves.

Considerable time and ongoing support usually are required to teach owners the technique for measuring blood glucose concentration. This monitoring option cannot always be introduced successfully, even if an owner is willing and enthusiastic to learn. In one study, only three of seven cat owners were able to generate a reliable serial blood glucose curve after training in the technique.[18] Samples can be obtained either from the marginal vein of the lateral pinna[16] or by collection of capillary blood from the medial pinna,[17] as described earlier. Once owners are familiar with the technique, they usually need some practice with their cat at home before they develop sufficient skill to generate a serial blood glucose curve. Although an owner's technique tends to improve with practice, it appears that cats rarely can be trained to accept the procedure if they will not tolerate it from the outset. If a cat resists blood collection from the pinna initially, its demeanor is unlikely to improve with repeated attempts.[18] Fortunately, the converse is true and cats that accept sampling from the start do not appear to develop aversion to the technique over time.[16]

Use of Continuous Glucose Concentration Monitoring Systems at Home

Sensors that measure subcutaneous or interstitial glucose concentration continuously are now being used to monitor glycemic control in human diabetic patients and have been used in diabetic cats. These methods of monitoring glycemia offer great clinical potential. The sensor is inserted and attached to the skin without sedation and the recording device held in place with a bandage. One limitation of this system is that it must be calibrated with blood glucose concentration two to three times every 24 hours, so some blood sampling during monitoring still is required. Initial assessment of a continuous glucose monitoring system in cats found positive correlation between interstitial and whole blood glucose concentrations.[34] Importantly, the system was shown to be valid for use in the home environment of diabetic cats and facilitated detection of hypoglycemia.[34,35] Further testing in diabetic cats is needed, however, before this method can be relied upon as the sole monitoring tool; a recent report stated that this device does not detect hypoglycemia reliably in insulin-treated human diabetics and performs well only at higher glucose levels.[36] Because a time lag exists for a change in blood glucose concentration to be reflected by interstitial glucose concentration, also undetermined is whether interstitial glucose concentration parallels blood glucose concentration in cats when blood glucose is changing rapidly, such as during the Somogyi phenomenon or postprandially.

OPTIONS FOR ASSESSMENT OF LONG-TERM GLYCEMIC CONTROL IN DIABETIC CATS

Assessment of glycemic control in managed diabetic cats requires awareness of the dynamic interplay between glucose toxicity, insulin resistance, dietary effects, stress hyperglycemia, counter-regulatory mechanisms, endogenous insulin secretion, and exogenous insulin action. In addition, unrelated concurrent disease processes can influence a cat's clinical signs and response to diabetic therapy at any time. Prediction of which cats will achieve remission of their diabetes or which will be difficult to control is impossible, and both of these outcomes can occur in the same cat at different times. Selection initially of a conservative insulin-dosing regimen, with gradual adjustment of dose over weeks to months, usually results in progressive improvement of clinical signs with low risk of hypoglycemia.

The fundamental approach to assessment of long-term glycemic control in diabetic cats is regular monitoring of historical and physical information coupled with judicious application of tests that provide objective glycemic data. The choice of monitoring options should be adapted to suit each individual case. The primary goal is to obtain as much information as possible from general physical examination of a cat and review of an owner's home records. Best results occur when veterinarians and owners cooperate as a team to achieve this goal.

Owners can provide daily and weekly records of clinical signs, whereas veterinary examination allows full evaluation of a cat's overall health status. Together, this permits determination of poor versus good glycemic control and the likelihood of concurrent disease. Regular reappraisal can identify changes over time.

Serum fructosamine concentration provides additional information on overall glycemic control for the preceding 2 to 3 weeks and may be a useful adjunct to physical and historical results in some cats.[37-39] Regular measurement of serum fructosamine concentration is recommended if owners cannot provide reliable records of a cat's clinical signs, particularly if limited information is available regarding the quantity of water consumed. It is especially valuable whenever stress-induced elevation of blood glucose concentration is suspected.[38-40]

High serum fructosamine concentrations (>500 µmol/L) indicate poor glycemic control but not whether the insulin dose needs to be increased or decreased. Making insulin dose rate changes on the basis of fructosamine measurements should be done with caution, because the fructosamine concentration does not give an indication of the nadir blood glucose concentration. Preferably, evaluation of changes in fructosamine concentrations should be conducted and related to a cat's clinical signs. Increased serum fructosamine concentration can occur with insulin overdose in cats, which should be suspected whenever periods of good glycemic control or episodes of hypoglycemia precede loss of diabetic control. The difference between baseline values and results obtained 2 to 4 weeks after an insulin dosage adjustment gives an indication of the initial glycemic response to the new dose. Dosage changes must occur no more frequently than every 1 to 2 weeks, and a cat's clinical signs must be monitored closely.

Measurement of glycosylated hemoglobin offers an alternative method of assessing overall glycemic control in cats.[41,42] However, it tends to be less useful clinically than serum fructosamine concentration because it indicates overall glycemic control over a longer period (2 to 3 months for glycosylated hemoglobin compared with 2 to 3 weeks for fructosamine) and is not always available commercially.

CONCLUSION

Clinical evidence of good glycemic control may result in little indication for performing serial blood glucose measurements in cats. This is particularly true if the volume of water consumed is normal, clinical hypoglycemia is not occurring, and the owner is monitoring for the presence or absence of urine glucose diligently. The principal reason for performing a serial blood glucose concentration curve in a diabetic cat is to evaluate whether the insulin dose can be increased without risk of inducing hypoglycemia. This requires assessment of the minimum or nadir blood glucose concentration resulting from the current insulin-dosing regimen. However, if an owner is not monitoring urine glucose, another reason to perform a blood glucose curve periodically is to detect subclinical hypoglycemia so that the insulin dose can be lowered appropriately.

As the time between insulin administration and the blood glucose nadir may vary daily, serial measurements always must be performed to ensure that the nadir is not missed. Predicting the timing of a diabetic cat's nadir on the basis of a previous serial blood glucose curve and obtaining a single sample at that time is unlikely to give a reliable result. Interpretation of serial blood glucose curves requires an understanding of the complex interactions involved in glucose homeostasis.[5,19] Additional indicators of overall glycemic control should be considered, such as changes in a cat's water intake and body weight, or the serum fructosamine level when appraising insulin dose by this method. The limitations of serial blood glucose curves include changes in blood glucose associated with inappetence and stress, and large day-to-day variability at home and in hospital. These limitations and the serious sequelae that may result from insulin overdose justify the need for a conservative approach to dosage recommendation.

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Chapter 21

Diagnostic Methods for Hyperthyroidism

Mark E. Peterson

The diagnosis of hyperthyroidism, one of the most common disorders affecting elderly cats, usually is straightforward and considered routine by most practitioners. Although diagnosis in most cats is not problematic, some cats suspected of having hyperthyroidism can be difficult to diagnose. Many of these cats have early or mild hyperthyroidism and show only mild clinical signs, whereas others appear to have more severe clinical features of hyperthyroidism but also have another obvious (or not so obvious) concurrent disease. The finding of hyperthyroidism developing concurrently with a nonthyroidal disease is not surprising, given the fact that many of these cats are elderly.

Diagnosis of hyperthyroidism in cats, especially when early and mild or when associated with concurrent nonthyroidal diseases, requires that the veterinarian collect a thorough history and physical examination and have a solid understanding of the physiology of the thyroid gland and the pituitary-thyroid axis. A better understanding of these pathophysiological mechanisms has led to the development and increasing use of free thyroid hormone concentrations and dynamic thyroid function tests in veterinary medicine. However, increased availability of these testing procedures requires the veterinarian to also have a good grasp of the pros and cons of the thyroid function tests used commonly in cats. This chapter highlights the available tests for hyperthyroidism in cats and their clinical applications.

GENERAL CONSIDERATIONS FOR DIAGNOSIS

Diagnosis of hyperthyroidism *must* take into account a cat's signalment, history, physical examination findings, and routine laboratory findings, in addition to results of specific thyroid function tests. Most cats with hyperthyroidism are middle-age to old-age, with only 5 per cent of cats being younger than 10 years of age at time of diagnosis.[1-5] Common clinical signs observed in hyperthyroid cats include weight loss, normal to increased appetite, hyperactivity, vomiting, diarrhea, polydipsia, and polyuria.[1-5] Because hyperthyroidism is now well recognized, veterinarians are diagnosing more cats at an early stage of the disease, in some cases even before owners realize that their cats are ill. Such cats with very mild hyperthyroidism may not have any obvious clinical signs or have only a single sign (e.g., mild weight loss despite a good appetite).[4,6-8] In hyperthyroid cats with concurrent disease (e.g., renal disease, hepatic disease, or neoplasia), weight loss remains a common clinical sign but may be accompanied by decreased rather than normal to increased appetite. In these cats, depression and weakness also may replace hyperexcitability or restlessness as dominant clinical features.

On physical examination, enlargement of one or both thyroid lobes can be detected in 80 to 90 per cent of cats with hyperthyroidism, an extremely important finding in making the diagnosis.[1-5] Although the thyroid gland usually is not palpable in normal cats, the finding of enlargement of one or both thyroid lobes on physical examination cannot be equated with hyperthyroidism, because thyroidal enlargement occasionally can be detected in cats without other clinical and laboratory evidence of the disease (see also Chapter 23).[9,10] Although some of these cats may remain euthyroid (at least for prolonged periods of time), many cats with thyroid gland enlargement eventually develop clinical and biochemical signs of hyperthyroidism as the thyroid nodules continue to grow and begin to oversecrete thyroid hormone.[6-10]

Other findings noted commonly on physical examination of hyperthyroid cats include evidence of weight loss, tachycardia, cardiac murmurs, and hyperkinesis.[1-5] These signs may not be pronounced in cats with mild or early hyperthyroidism. In hyperthyroid cats with concurrent disease, other clinical signs caused by the second disease may predominate.

RESTING (BASAL) SERUM THYROID HORMONE TESTS

Total Thyroxine and Triiodothyronine Concentrations

Measurement of serum total thyroxine (T_4) and triiodothyronine (T_3) concentrations is used commonly to assess thyroid

gland function in cats. High basal serum T_4 and T_3 concentrations are the biochemical hallmarks of hyperthyroidism; the finding of high concentrations of T_4 or T_3 is extremely specific for diagnosis, with no false-positive results reported in cats.[1-5,11]

Assay Techniques for Thyroid Hormone Determination

Assays for measurement of serum total T_4 and T_3 concentrations are readily accessible, relatively cheap, and do not involve specific sampling requirements. Most veterinarians send samples for T_4 or T_3 measurement to commercial laboratories that use a variety of accepted assay procedures to measure serum thyroid hormone concentrations. Radioimmunoassay (RIA) generally is considered to be the preferred or "gold standard" method, but nonisotopic and automated techniques, such as chemiluminescent enzyme immunoassay, are becoming increasingly popular.[4,11-14] Generally, these nonisotopic methods correlate reasonably well with results of RIA analysis; however, each testing methodology is susceptible to sporadic errors that can result in outlying T_4 or T_3 values, in addition to technology-specific trends that could produce an overall bias when results from different assay methods are compared.

Thyroid hormone assays intended for human serum are acceptable but must be validated fully for use with feline serum, and modified to allow for measurement of the lower circulating concentrations of hormone in this species. In addition, each laboratory should establish its own reference ranges for feline T_4 and T_3 concentrations based upon the assay procedures used to measure the hormone concentrations at their site. Sending samples to a human reference laboratory is not recommended, because these laboratories rarely have validated their assays for use in cats nor have they established reference ranges for feline T_4 and T_3. Both RIA and chemiluminescence assay techniques appear to be equally as accurate as long as the assay has been validated for use in cats, and cat-specific reference ranges have been established for that particular assay technique.

Semiquantitative assays for total T_4 that are suitable for in-hospital testing also may be useful in the diagnosis of hyperthyroidism in cats.[4,13] Such commercial kits allow practitioners to measure T_4 concentrations in-house while a client waits for the results. However, in one study that compared an in-house enzyme-linked immunosorbent assay (ELISA) T_4 kit to a commercial T_4 RIA in cats, substantial discrepancies in serum T_4 concentrations were demonstrated, which led the investigators to conclude that the in-house kit was not accurate for use in cats.[14] In contrast to that study, we found a clinical agreement between the serum T_4 concentrations measured by the same in-house ELISA T_4 kit and commercial RIA assay techniques.[13] Further study of these ELISA T_4 kits is warranted to determine if they can provide a reasonable in-house screening test for thyroid gland disorders of cats that is comparable to the standard RIA techniques for measuring serum T_4 concentrations.

As might be expected, none of the serum T_4 assays always provides diagnostic results in all cats with hyperthyroidism. No matter what total T_4 assay is used, the clinician should consider use of other serum thyroid tests (e.g., free T_4) to confirm the diagnosis of hyperthyroidism in cats in which the clinical signs are not consistent with the condition, or if a thyroid nodule is not easily palpable.

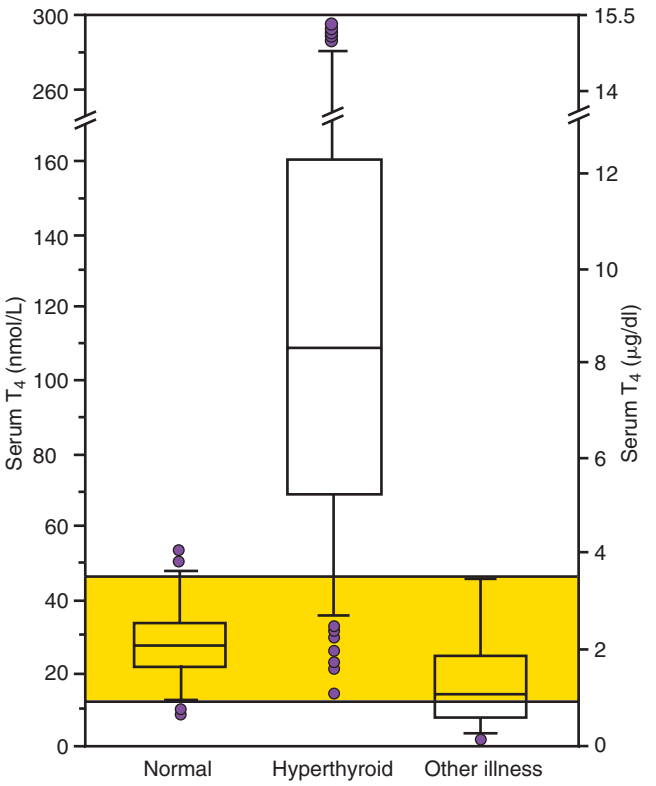

Figure 21-1. Box plots of the serum concentrations of total T_4 concentrations tests in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease. For each box plot, the T-bars represent the main body of data, which in most instances is equal to the range. The box represents the interquartile range (i.e., the 25th percentile to 75th percentile range or the middle half of the data). The horizontal bar in the box is the median. Outlying data points are represented by open circles. The shaded area indicates the reference interval, which was established by use of the nonparametric method of percentile estimates with confidence intervals to determine the 2.5th percentile to 97.5th percentile range for results from the clinically normal cats. (From Peterson ME, Melian C, Nichols R: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease. J Am Vet Med Assoc 218:529-536, 2001.)

Diagnostic Sensitivity of Thyroid Hormone Determination

The serum concentrations of total T_4 and T_3 are highly correlated in hyperthyroid cats, but measurement of total T_4 is preferred over T_3 because of its better diagnostic sensitivity.[1-5,11] More than 30 per cent of hyperthyroid cats have serum total T_3 concentrations within the reference range, whereas only 10 per cent of all hyperthyroid cats have normal serum T_4 concentrations (Figures 21-1 and 21-2).[11] Most cats with normal total T_3 concentrations have early or mild hyperthyroidism and, accordingly, corresponding serum total T_4 concentrations usually are only just above the reference range. Therefore the normal T_3 concentrations likely would increase into the thyrotoxic range in these cats if the disorder were allowed to progress untreated. A possible explanation for normal circulating T_3 concentrations in cats with mild hyperthyroidism is that, as thyroid hormone production begins to increase in hyperthyroid cats, a compensatory decrease occurs in peripheral conversion of T_4 to the more active T_3. In addition, T_3 is located mainly intracellularly,

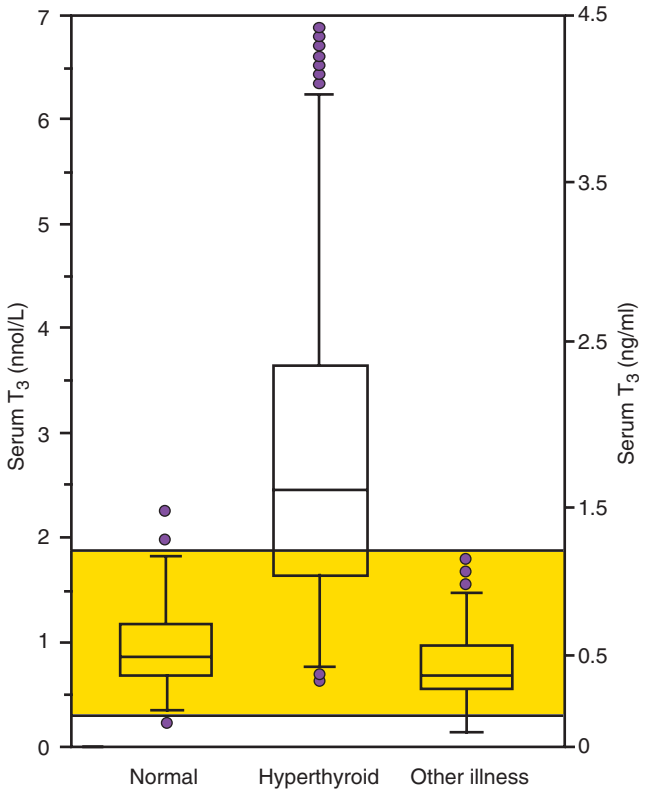

Figure 21-2. Box plots of the serum concentrations of T_3 concentration tests in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease. See Figure 21-1 for key. (From Peterson ME, Melian C, Nichols CE: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease. J Am Vet Med Assoc 218:529-536, 2001.)

so serum concentrations may not be an accurate reflection of what is present in the body. In any case, measurement of serum T_3 concentration alone cannot be strongly recommended as a diagnostic test for hyperthyroidism in cats.[2,4,11]

Most hyperthyroid cats exhibit persistently high circulating total T_4 concentrations, with values up to approximately 20 times the upper limit of the reference range. However, a significant proportion of hyperthyroid cats (approximately 10 per cent of all cases and 40 per cent of cases with mild hyperthyroidism) have serum total T_4 concentration within the reference range (see Figure 21-1).[2,11] Such normal T_4 concentrations usually are within the mid to high end of the reference range. Therefore, although serum T_4 is the best single test used to diagnose hyperthyroidism in cats, the disease cannot be excluded by the finding of a single, normal total T_4 concentration.[2-8,11]

The finding of normal serum thyroid hormone concentrations in cats with clinical signs suggestive of hyperthyroidism can be problematic. How can a cat develop clinical signs (albeit mild in many cases) of hyperthyroidism when serum thyroid hormone concentrations remain within the reference range? Two explanations have been proposed to explain the findings of normal serum thyroid hormone concentrations in cats with hyperthyroidism: (1) fluctuation of T_4 and T_3 in and out of the normal range[15] and (2) suppression of high serum T_4 and T_3 concentrations into the normal range because of concurrent nonthyroidal illness.[11,16,17] Approximately 20 to 30 per cent of hyperthyroid cats that have circulating total T_4 concentrations within the reference range have an identifiable concurrent illness, and the remaining majority usually are classified as mild or early cases.[11,17]

Fluctuation of T_4 and T_3 Over Time

Thyroid hormone concentrations in cats with hyperthyroidism may fluctuate considerably over time.[15] In cats with thyroid hormone concentrations well above the normal range, this fluctuation does not appear to be of great clinical or diagnostic significance. However, in cats with mild hyperthyroidism, the degree of serum T_4 and T_3 fluctuation that can occur—into the reference range in some cats—affirms that a diagnosis of hyperthyroidism cannot be excluded on the basis of the finding of a single normal to high-normal serum T_4 or T_3 result. In cats with clinical signs consistent with hyperthyroidism (and especially in cats with palpable thyroid nodules), more than one serum T_4 determination could be required to confirm a diagnosis.

Suppression of T_4 and T_3 as a Result of Nonthyroidal Disease

In hyperthyroid cats with concurrent nonthyroidal illness (e.g., renal disease, diabetes mellitus, systemic neoplasia, primary hepatic disease, and other chronic illnesses), the effects of the nonthyroidal disease suppress the high serum thyroid hormone concentrations to various degrees. Although the effect of mild nonthyroidal disease appears to have little clinically significant suppressive effect on the high total T_4 and T_3 concentrations associated with hyperthyroidism, moderate to severe nonthyroidal diseases typically lower the total T_4 concentrations, sometimes into the mid-normal to high-normal range.[11,16,17] Occasionally, serum total T_4 concentrations can even be suppressed to the low end of the reference range in hyperthyroid cats that are extremely ill.[11,18] In such cases, the concurrent illness dictates the prognosis, and the existence of hyperthyroidism is of lesser clinical significance.

Because severe nonthyroidal illness would be expected to decrease serum thyroid hormone concentrations into the low to undetectable range in sick cats without concurrent hyperthyroidism,[4,5,11,16] concomitant hyperthyroidism should be suspected in any middle-age to old-age cat with severe nonthyroidal illness and serum T_4 and T_3 concentrations in the mid to upper half of the reference range, especially if signs of hyperthyroidism also are present. Upon stabilization of, or recovery from, the concurrent nonthyroidal disorder, serum thyroid hormone concentrations in these cats with hyperthyroidism increase again from the normal range to above the reference range limits.

When the clinician suspects hyperthyroidism in a cat but the serum T_4 (and T_3) concentration is not high, the first steps should always be to repeat the basal T_4 measurement and rule out nonthyroidal illness (through a complete physical examination, routine blood tests, and diagnostic imaging, as needed). Because hormone concentrations vary greater over a period of days than over a period of hours,[15] the second serum T_4 determination should be made at least 1 to 2 weeks later. If the serum T_4 results are persistently in the normal to high-normal range and hyperthyroidism is still suspected, determination of a free T_4 concentration (by dialysis) or provocative testing with a T_3 suppression test or thyrotropin-releasing hormone (TRH) stimulation test is recommended.[11,19-23]

Free Thyroid Hormone Concentrations

Circulating thyroid hormones can be either bound to carrier proteins or free (unbound) in plasma. Most commercial T_4 and T_3 assays measure total concentrations, both free and protein-bound. Because only the free fraction of thyroid hormone is available for entry into the cells, free T_4 determinations should provide a more consistent assessment of thyroid gland status than total T_4 concentrations.[24,25] Also, free T_4 concentrations are influenced to a lesser degree by factors such as nonthyroidal illness that may falsely lower total T_4 concentrations.

Serum free T_4 and total T_4 concentrations are highly correlated in cats with hyperthyroidism. However, serum free T_4 concentrations, as measured by equilibrium dialysis, are more consistently (more than 98 per cent of cases) elevated in hyperthyroid cats (Figure 21-3).[11] More significantly, serum free T_4 concentrations are high in 95 per cent of hyperthyroid cats in which total T_4 concentrations are within the reference range (Figure 21-4).[11]

Although measurement of free T_4 concentration is clearly the most sensitive diagnostic test for hyperthyroidism, some valid arguments exist against its use as a sole replacement for total T_4 determinations. Free T_4 concentrations are only truly measured by techniques such as equilibrium dialysis or ultrafiltration.[24,25] Controversy surrounds the validity of other methods, particularly those involving analogues, for measuring free T_4 concentrations accurately. In general, nondialysis techniques for free T_4 determination are less accurate, often underestimate the free T_4 concentration, and offer little if any advantage over measurement of total T_4 concentration.[24,25]

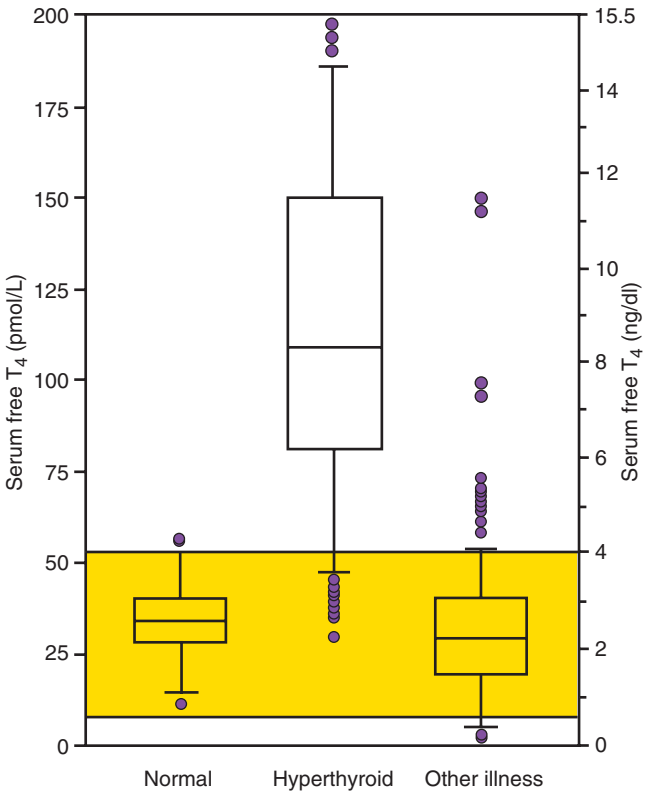

Figure 21-3. Box plots of the serum concentrations of free T_4 concentrations tests in 172 clinically normal cats, 917 cats with untreated hyperthyroidism, and 221 cats with nonthyroidal disease. See Figure 21-1 for key. (From Peterson ME, Melian C, Nichols CE: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease. J Am Vet Med Assoc 218:529-536, 2001.)

Other major disadvantages of free T_4 by dialysis are that the technique is much more expensive than a total T_4 determination and is not offered by all commercial laboratories. Measurement of free T_4 by dialysis also is subject to more errors than that of total T_4 because of sample handling during transport to the laboratory. For example, when stored at 37° C for 7 days, measured concentrations of free T_4 by dialysis increased by 160 per cent.[26] This increase in apparent free T_4 concentration results from either degradation of binding globulins or loss of binding globulin affinity for T_4.

The most important disadvantage of use of the free T_4 determination, however, is the loss of diagnostic specificity seen occasionally in sick, euthyroid cats. Up to 12 per cent of cats with nonthyroidal illness that do not have hyperthyroidism have high free T_4 concentrations for reasons that are unclear (see Figure 21-3).[11,27] Therefore caution is advised in the use of serum free T_4 measurements by equilibrium dialysis as the sole diagnostic test for cats with hyperthyroidism. To avoid a misdiagnosis of hyperthyroidism, free T_4 always should be evaluated in conjunction with the total T_4 concentration (in addition to the cat's signalment, history, physical examination findings, and routine laboratory findings). In general, the combination of a high free T_4 value with a low total T_4 concentration (<10 nmol/L or <0.8 μg/dl) is indicative of nonthyroidal illness, whereas a high free T_4 value with a high-normal T_4 concentration (>25 nmol/L or >3.0 μg/dl) is suggestive of hyperthyroidism (see Figures 21-2 and 21-3).[11] Cats with high free T_4 with low-normal total T_4 concentrations usually have mild to moderate nonthyroidal illness alone, although the serum total T_4 concentration in hyperthyroid cats with severe, concurrent nonthyroidal illness also can be suppressed occasionally to the lower end of the reference range limits.

In all hyperthyroid cats with a high serum total T_4 concentration, free T_4 concentration also will be high, and its measurement adds no further diagnostic information.[4,11] Therefore, given the expense of free T_4 measurement, coupled with the high prevalence of high total T_4 concentrations in hyperthyroid cats (approximately 90 per cent), it is more cost-effective initially to measure total T_4 concentration alone. If the total serum T_4 is normal but hyperthyroidism is still suspected, only then should consideration be given to measurement of the corresponding free T_4 concentration.

In summary, determination of a free T_4 concentration is useful in diagnosis of hyperthyroidism, especially in cats in which hyperthyroidism is suspected but total T_4 and T_3 concentrations remain within reference range limits. However, because a high free T_4 concentration develops in some cats with nonthyroidal disease, diagnosis of hyperthyroidism should *never* be based solely on the finding of a high free T_4 concentration alone. The finding of a high free T_4 concentration (despite a normal T_4) in a cat with a consistent history (e.g., weight loss despite good appetite) and physical examination findings (e.g., palpable thyroid nodule) would support the diagnosis of hyperthyroidism. If a thyroid nodule cannot be palpated, however, or if another moderate to severe illness is known to be present, confirmation of hyperthyroidism with a dynamic thyroid function test is recommended, such as the T_3 suppression or TRH stimulation test, which remain the gold standards for diagnosis of occult hyperthyroidism in cats.[19-23]

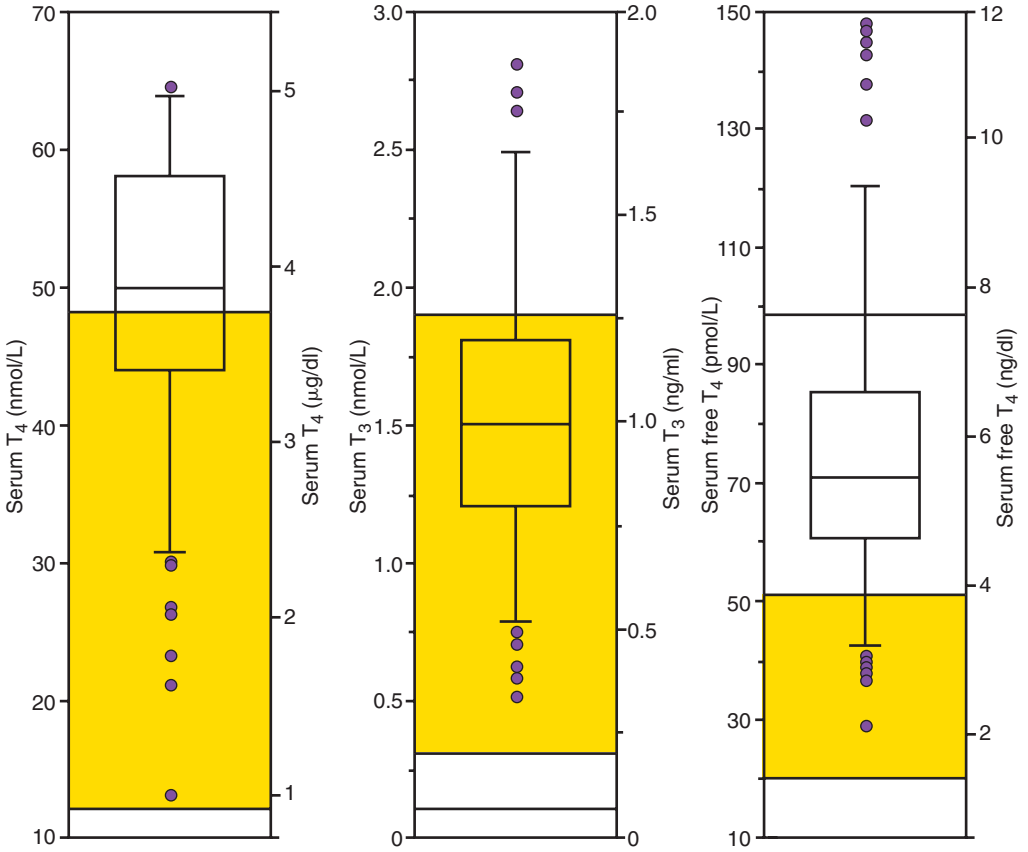

Figure 21-4. Box plots of the serum total T_4, T_3, and free T_4 concentrations in 205 cats with mild hyperthyroidism (defined as a total T_4 concentration <66 nmol/L or <5 µg/dl). See Figure 21-1 for key. (From Peterson ME, Melian C, Nichols CE: Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease. J Am Vet Med Assoc 218:529-536, 2001.)

Alternately, it may not be unreasonable to treat any known underlying nonthyroidal disease and monitor total T_4 and free T_4 concentrations at 2-month to 3-month intervals, because the thyroid nodule(s) will continue to enlarge and total T_4 concentrations eventually will rise above reference range limits in cats with hyperthyroidism.

PROVOCATIVE OR DYNAMIC SERUM TESTS

In the great majority of hyperthyroid cats that have "normal" total T_4 concentrations, the identification of concurrent disease, repeat total T_4 determination, or simultaneous measurement of free T_4 allows confirmation of the diagnosis. Further diagnostic tests rarely are required. However, dynamic thyroid function tests are recommended to help the diagnosis of hyperthyroidism in some cats. Protocols and interpretive advice for these tests are outlined in Table 21-1. In general, these provocative dynamic or thyroid function tests are needed only in, and should be considered only in, cats with clinical signs suggestive of hyperthyroidism when repeated total T_4 concentrations remain within reference range and free T_4 analysis is unavailable or diagnostically unhelpful.

Thyroid Hormone (Triiodothyronine) Suppression Test

Inhibition of pituitary thyroid-stimulating hormone (TSH) secretion by high circulating concentrations of thyroid hormone is a characteristic feature of normal pituitary-thyroid regulation.[28] Therefore administration of T_3 to normal cats leads to a decrease in TSH secretion, which in turn causes diminished T_4 secretion. In contrast, when thyroidal function is autonomous (i.e., independent of TSH secretion), administration of thyroid hormone has little or no effect on serum T_4 concentration, because TSH secretion already has been suppressed chronically. This is invariably true with clinical hyperthyroidism. Therefore, when the T_3 suppression test is performed in normal cats, a marked fall occurs in serum T_4 concentrations after exogenous T_3 administration. In contrast, when the test is performed in cats with hyperthyroidism, even in cats with only slightly high or high-normal resting serum T_4 concentrations, minimal, if any, suppression of serum T_4 concentrations is seen.

To perform the T_3 suppression test in cats, a blood sample is drawn for determination of basal serum concentrations of total T_4 and T_3.* This blood sample should be centrifuged and the serum removed and kept refrigerated or frozen. Owners are instructed to administer T_3 orally (liothyronine, Cytomel, Jones Medical Industries, Pointe Claire, Quebec) beginning the following morning at a dosage of 25 µg q8h for 2 days (see Table 21-1). On the morning of the third day, a seventh 25-µg dose of liothyronine is given and the cat returned to the veterinary clinic within 2 to 4 hours for serum T_4 and T_3 determinations. Both the basal (day 1) and post-liothyronine serum samples

*References 3-5, 19, 20, 22, 23.

Table 21-1 | **Commonly Used Protocols for Dynamic Thyroid Function Tests in Cats**

	T_3 SUPPRESSION TEST	TRH STIMULATION TEST	TSH STIMULATION TEST	
Drug	Liothyronine (Cytomel)	TRH	Bovine TSH	Human TSH
Dose	25 µg q8h for 7 doses	0.1 µg/kg	0.5 IU/kg	0.025-0.20 mg/cat
Route	Oral	Intravenous	Intravenous	Intravenous
Sampling Times	Before and 2-4 hours after last dose	Before and at 4 hours	Before and at 6 hours	Before and at 6-8 hours
Assay	Total T_4 and T_3	Total T_4	Total T_4	Total T_4
Interpretation*:				
Euthyroidism	T_4 <20 nmol/L with >50% suppression	>60% increase in T_4	>100% increase in T_4	>100% increase in T_4
Hyperthyroidism	T_4 >20mol/L with <3% suppression	<50% rise in T_4	Minimal to no increase	Not determined

*Values quoted for interpretation are guidelines only. Each individual laboratory should furnish its own reference range.

should be submitted to the laboratory together to eliminate the effect of interassay variation in hormone concentrations.

Regarding interpretation of T_3 suppression test results, we find that the absolute serum T_4 concentration after liothyronine administration is the best means of distinguishing hyperthyroid cats from normal cats or cats with nonthyroidal disease (see Table 21-1).[19] Cats with hyperthyroidism have post-liothyronine serum T_4 concentrations greater than 20 nmol/L (~ 1.5 µg/dL), whereas normal cats and cats with nonthyroidal disease have T_4 values less than 20 nmol/L. The three groups of cats may exhibit a great deal of overlap of the per cent decrease in serum T_4 concentrations after liothyronine administration, but suppression of 50 per cent or more only occurs in cats without hyperthyroidism.

Serum T_3 concentrations, as part of the T_3 suppression test, are not useful in the diagnosis of hyperthyroidism per se. However, measurement of basal and post-liothyronine serum T_3 concentrations should be done to monitor owner compliance with giving the drug. If inadequate T_4 suppression is found, but serum T_3 concentrations do not increase by at least 10 per cent above the basal T_3 concentration after treatment with liothyronine, problems with owner compliance should be suspected and the test result considered questionable.

Overall, the T_3 suppression test is useful for diagnosis of mild hyperthyroidism in cats, but the disadvantages are that it is a relatively long test (3 days), owners are required to give multiple doses of liothyronine, and cats must swallow the tablets.[19,20] If the liothyronine is not administered properly, circulating T_3 concentrations will not rise to decrease pituitary TSH secretion, and the serum T_4 value will not be suppressed, even if the pituitary-thyroid axis is normal. Failure of a cat to ingest the liothyronine could result in a false-positive diagnosis of hyperthyroidism in a normal cat or cat with nonthyroidal disease.

Thyrotropin-Releasing Hormone (TRH) Stimulation Test

The TRH stimulation test measures the serum T_4 response to administration of TRH. In clinically normal cats, the administration of TRH causes an increase in TSH secretion and serum T_4 concentrations, whereas in cats with hyperthyroidism, the TSH and serum T_4 response to TRH is blunted or totally absent.[28] The lack of response is due to chronic suppression of TSH secretion in cats with hyperthyroidism that cannot be overcome by a single injection of TRH.

To perform a TRH stimulation test, blood is collected for serum T_4 determination before and 4 hours after intravenous administration of 0.1 mg/kg TRH (Relefact TRH, Hoechst-Roussel Pharmaceuticals, Kansas City, Missouri; Thypinone, Abbott Diagnostics, Abbott Park, Illinois).[2-5,21,22] Cats with hyperthyroidism show little, if any, rise in serum T_4 concentrations after administration of TRH, whereas a consistent rise of serum T_4 concentrations (approximately twofold rise) occurs after TRH administration in clinically normal cats and cats with nonthyroidal disease (see Table 21-1). The serum T_3 response to TRH is less helpful in separating normal from hyperthyroid cats, because many normal cats have only a small and inconsistent rise in serum T_3 concentrations after TRH administration. Therefore, although basal T_3 concentration might be helpful in diagnosis of hyperthyroidism in some cats, we do not recommend determination of the serum T_3 response as part of the TRH stimulation test.[21,22]

Regarding interpretation of the TRH stimulation test results, the relative rise (per cent increase) in serum T_4 concentration after administration of TRH is the best (most sensitive) criterion for predicting whether or not cats are hyperthyroid (see Table 21-1). A per cent rise in serum T_4 of less than 50 per cent is consistent with hyperthyroidism, whereas a value of greater than 60 per cent is seen in normal cats and cats with nonthyroidal illness; values between 50 and 60 per cent are equivocal or borderline responses.[21]

Both the TRH stimulation test and the T_3 suppression test are best for diagnosing cats with mild or early hyperthyroidism that do not have any concurrent illnesses. In hyperthyroid cats that have developed marked suppression of the circulating T_4 concentrations into the normal (or subnormal) range because of the effects of concurrent moderate to severe nonthyroidal illness, the diagnostic accuracy of both of these tests will decrease. In one study, for example, investigators found that the TRH stimulation test failed to differentiate a group of critically ill hyperthyroid cats from a group of euthyroid cats with nonthyroidal illnesses.[18]

Studies have shown a close relationship between the presence (or absence) of suppressed serum T_4 concentrations in response to T_3 suppression and stimulated T_4 values in response to TRH stimulation.[21] Therefore, although the two tests evaluate the pituitary-thyroid axis in different ways, findings indicate that the two screening tests provide similar information and probably can be used interchangeably for diagnosing mild hyperthyroidism in cats.

Advantages of the TRH stimulation test over the T_3 suppression test include the shorter time needed to perform the test (4 hours instead of 3 days), and the fact that the TRH stimulation test is not dependent upon the owner's ability to administer oral medication. The major disadvantage of the TRH

stimulation test in cats is that side effects (e.g., salivation, vomiting, tachypnea, and defecation) occur almost invariably immediately after administration of the TRH. Reportedly, TRH evokes these effects in cats via activation of central cholinergic and catecholaminergic mechanisms and by a direct neurotransmitter effect of TRH itself on specific central TRH binding sites.[29-31] Fortunately, all of the adverse side effects associated with TRH administration are transient and resolve completely by the end of the 4-hour test period. Therefore, at the discretion of the veterinarian, owners need not be exposed to the occurrence of these side effects in their cats.

Thyroid Stimulating Hormone (TSH) Stimulation Test

Exogenous TSH is a potent stimulator of thyroid hormone secretion. However, serum total T_4 concentrations show little or no increase after exogenous bovine TSH administration in hyperthyroid cats (see Table 21-1).[1,4,32] Presumably this is because the thyroid gland of affected cats secretes thyroid hormones independently of TSH control, or that T_4 already is being produced at a near maximal rate with limited reserve capacity.

Hyperthyroid cats with serum total T_4 concentrations that are equivocally high tend to show results that are indistinguishable from healthy cats.[32] In addition, bovine TSH is no longer available for parenteral administration. Recombinant human TSH has been evaluated in healthy cats and, although it appears to be a safe and effective replacement for bovine TSH, it has not yet been evaluated in hyperthyroid cats and has a significant cost implication.[33] Overall, because of its poor diagnostic performance and high cost, the TSH stimulation test is not recommended as a diagnostic test for hyperthyroidism.

THYROIDAL IMAGING/RADIOISOTOPE UPTAKE TEST

Hyperthyroid cats usually exhibit an increased thyroidal uptake of radioactive iodine (^{123}I or ^{131}I) or technetium-99m as pertechnetate ($^{99m}TcO_4^-$).[1,34,35] Percentage uptake or increased thyroid:salivary ratio may be calculated, and both are correlated strongly with circulating thyroid hormone concentration and provide an extremely sensitive means of diagnosing hyperthyroidism.[35]

However, apart from expense and the difficulties in dealing with radioisotopes, sophisticated computerized medical equipment is required. In addition, anesthesia generally is required, and caution is advised in interpretation of results from cats treated previously with antithyroid drugs because radioisotope uptake can be enhanced for several weeks after drug withdrawal.[36] Qualitative thyroid imaging is most useful in assessment of thyroid involvement before surgical thyroidectomy.[1,3,4] Similarly, high-resolution ultrasonography may provide an alternative to thyroid imaging, but larger studies are required for its evaluation.[37]

Although thyroid uptake measurements and imaging may be useful in some cats with suspected hyperthyroidism, the diagnosis almost always can be made more easily and in a manner that is less stressful for the cat by measuring serum T_4 and free T_4 concentrations, as described.[11] If serum concentrations of serum T_4 and free T_4 are within reference range limits (especially if concentrations remain normal when repeated one or twice over a 3-month period), clinical hyperthyroidism is highly unlikely and thyroidal uptake measurements or thyroid imaging probably are not warranted in such cats.

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Chapter 22

Update on Treatment of Hyperthyroidism

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Hyperthyroidism is the most commonly recognized endocrinopathy of cats. A benign thyroid adenoma or adenomatous hyperplasia present in one, or more commonly both, lobes of the thyroid gland is responsible for the vast majority of recognized cases of hyperthyroidism in cats. Fewer than 2 per cent of cases occur as a result of a functional thyroid carcinoma.[1] To date, therapies for treatment of hyperthyroidism have been aimed at inhibition of thyroid hormone development via medical therapy or the ablation or physical removal of thyroid tissue via surgery, radiation, chemical, or heat application.

MEDICAL THERAPY

Thioureylene Drugs

Historically, medical treatment of hyperthyroidism most commonly has used thioureylenes, a structurally related group of antithyroid drugs, which includes propylthiouracil, methimazole, and carbimazole. These drugs are concentrated actively within the thyroid gland after administration.[2] They are not cytotoxic in nature and are unable therefore to resolve hyperthyroidism permanently. The ability of thioureylenes to inhibit thyroid hormone biosynthesis involves complex interactions with thyroid peroxidase and thyroglobulin, many of which are still poorly understood.[2] Thioureylenes may serve as competitive substrates for thyroid peroxidase, an enzyme that catalyzes the incorporation of oxidized iodide into tyrosine residues in thyroglobulin molecules and couples iodotyrosines to form thyroxine (T_4) (Figure 22-1).[2-4] As a result, thioureylenes are iodinated, which diverts iodine from the synthesis of thyroid hormones and prevents their formation.[3-5]

Propylthiouracil

Propylthiouracil was the first thioureylene used successfully in the treatment of hyperthyroidism in cats.[6] In addition to the mechanisms of action described above, propylthiouracil has the additional benefit of inhibiting conversion of thyroxine (T_4) to the more biologically active thyronine (T_3), a reaction that occurs in peripheral tissues.[2-4] However, in addition to causing anorexia, vomiting, and lethargy, propylthiouracil has been associated with a high incidence of severe side effects, including agranulocytosis and thrombocytopenia.[7-9] Because of the severity of the adverse effects, propylthiouracil is no longer recommended for treatment of feline hyperthyroidism.

Methimazole

Methimazole is safer than propylthiouracil for the management of feline hyperthyroidism and is readily available in the United States. Oral as well as topical administration (see Chapter 18) has been shown to be successful in normalizing serum thyroid hormone levels in hyperthyroid cats.[1,18,21] Methimazole is used commonly for long-term medical management of hyperthyroidism. Additionally, short-term therapy is useful for stabilization and for assessment of renal function before pursuit of a more permanent treatment such as surgery or radioactive iodine therapy. After normalization of thyroid hormone concentrations, glomerular filtration rate may decrease, potentially exacerbating or "unmasking" underlying renal disease.[1] If renal parameters improve or remain static after a methimazole treatment trial, a more permanent treatment option may be pursued safely. Additionally, even if renal parameters worsen slightly but the clinical status of the cat improves because of remission of the hyperthyroidism and no clinical signs of renal disease/failure develop, definitive therapy can be sought.

In human beings, methimazole has a plasma half-life of 5 to 6 hours, with the majority excreted through the urine within 48 hours of administration.[2,5] In cats, the plasma half-life is similar, ranging from less than 3 hours to approximately 6 hours.[10,11] Methimazole's activity, however, correlates with intrathyroidal drug concentrations, not the plasma half-life. Because methimazole, like other thioureylenes, is concentrated in thyroidal tissue, the biological effect of the drug exceeds its plasma half-life.[2,5]

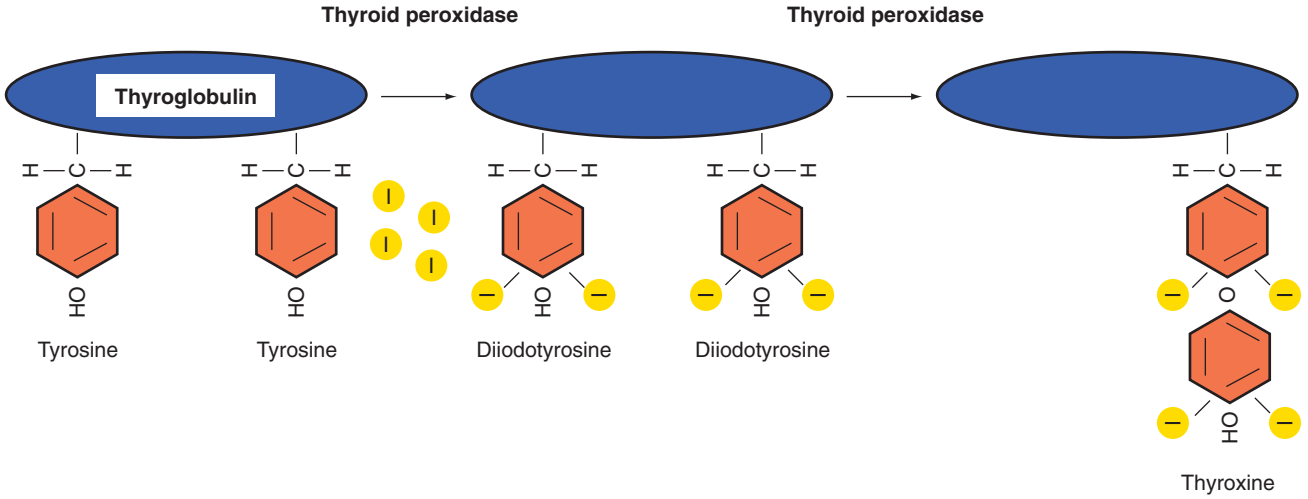

Figure 22-1. Actions of thyroid peroxidase in thyroid hormone production. Tyrosine residues on the thyroglobulin molecule are iodinated to form monoiodotyrosine or diiodotyrosine. These iodinated tyrosine residues then are joined together to form thyroxine (T_4) or triiodothyronine (T_3).

Various recommendations have been made regarding initial dosing of methimazole, ranging from 2.5 mg to 15 mg/day in divided doses q8-12h.[1,10,12-15] Most cats require between 5 and 10 mg/day of methimazole to control their disease[1,18]; twice or three times daily administration is the most effective.[16] Side effects may be less severe and less common with lower doses of methimazole. Therefore a conservative approach to dosing with an initial dose not exceeding 5 mg per day has been recommended by some authors, and an even lower initial dose (2.5 mg/day) should be used in cases of concern regarding side effects of therapy, such as concurrent renal insufficiency.[1] When therapy is initiated with lower doses, gradual increases in dosage usually are required for adequate disease control. If no adverse effects have occurred after an initial 2-week period, the dose may be increased gradually in increments of 2.5 mg per day as needed every 2 weeks.[1] Once an effective dose has been achieved, serum total T_4 concentrations fall to within the lower half of the reference range (the target range for cats receiving methimazole) in most cats within 1 to 3 weeks.[1,17] Dosages above 12.5 to 15 mg/day rarely are required for adequate disease control because drug resistance is rare.[1] Failure to respond to methimazole most frequently is a result of owners' failure to administer the drug successfully to their cats.[1]

Various adverse effects may occur with methimazole therapy administered either orally or transdermally (Table 22-1). Approximately 10 to 20 per cent of cats have drug-related problems.[15] Most side effects occur within the first 3 months of therapy.[1,15,18,19] The most common adverse effects are anorexia, vomiting, and lethargy, which occur in up to 20 per cent of cats but may be transient and resolve with ongoing therapy.[15,18] Perhaps use of the conservative treatment protocol discussed above may reduce the incidence of adverse reactions significantly to less than 3 per cent of treated cats, but this has not been proven.[1] Mild hematological changes (e.g., eosinophilia, lymphocytosis, and mild leukopenia) also may be observed transiently.[1,15,18] Possible severe side effects include thrombocytopenia, bleeding diathesis, agranulocytosis, hepatopathy, and idiosyncratic dermatological reactions that result in facial pruritus.[1,15,18] These reactions are uncommon, affect less than 3 per cent of patients,[18,20] and require cessation of methimazole therapy. Abnormalities resolve soon after drug therapy is discontinued. If severe cytopenias are present, supportive care, such as administration of blood transfusions, colony-stimulating factors, or broad-spectrum antibiotics, may be required before resolution. Cats with methimazole-induced hepatopathy also may require appropriate supportive care. Cats with facial excoriations may respond to glucocorticoids and antihistamine therapy. As these more severe drug-related complications reoccur typically with reintroduction of methimazole, an alternative therapy should be pursued.

Additional severe complications such as hemolytic anemia, myasthenia gravis, and cold agglutinin-like disease have been reported rarely with methimazole use. Approximately 50 per cent of all cats treated with long-term methimazole therapy develop positive serum antinuclear antibody titers,[15] but no associated clinical effects have been reported.

Topical administration of methimazole compounded in a pluronic lecithin organogel can be an effective means of treatment in hyperthyroid cats.[21] Although oral administration of methimazole usually is effective in lowering serum total T_4 to within the target range within approximately 2 weeks of administration initiation, topical therapy may take longer to be successful. In one study, most hyperthyroid cats' disease was controlled after 4 weeks of topical methimazole administration.[21] The incidence of adverse gastrointestinal effects may be decreased significantly with topical methimazole therapy as compared with the oral route[21]; however, other adverse effects appear to occur with similar frequency (see Table 22-1).[21] Further information regarding topical methimazole therapy can be found in Chapter 18.

Carbimazole

Carbimazole is available in the United Kingdom, Europe, Australia, and Canada, but not in the United States. It is a carbethoxy derivative of methimazole that is converted rapidly

Table 22-1 | **Adverse Drug-Related Reactions Associated with Medical Treatment of Hyperthyroidism**

REACTION	ORAL METHIMAZOLE THERAPY: APPROXIMATE PER CENT OF CATS AFFECTED	TOPICAL METHIMAZOLE THERAPY: APPROXIMATE PER CENT OF CATS AFFECTED	ORAL CARBIMAZOLE THERAPY: APPROXIMATE PER CENT OF CATS AFFECTED
Vomiting, anorexia and lethargy	10-20[15]	4[21]	5-10[1,23]
Eosinophilia	10[15]	Unknown, presumed similar to oral methimazole[21]	5[15]
Lymphocytosis	7[15]	Unknown, presumed similar to oral methimazole[21]	3-5[15,23]
Leukopenia	5[15]	Unknown, presumed similar to oral methimazole[21]	3-5[15,23]
Thrombocytopenia	2-3[15]	Unknown, presumed similar to oral methimazole[21]	Never reported
Agranulocytosis	1-2[15]	Similar to oral methimazole[21]	Never reported
Positive ANA titer	20- >50[1,15]	Unknown	Never reported
Positive Coombs' test	1.5[15]	Unknown	Never reported
Hepatopathy	1-2[15]	Similar to oral methimazole[21]	Never reported
Facial excoriations	2-5[15]	Similar to oral methimazole[21]	Rare[15]
Bleeding diathesis	2-3[15]	Unknown	Never reported
Myasthenia gravis	<0.5[15]	Unknown	Never reported
Hemolytic anemia	<0.5[15]	Unknown	Never reported
Cold-agglutinin–like disease	<0.5[15]	Unknown	Never reported

into methimazole in vivo in human beings and cats.[14,22] Because lower maximal serum methimazole concentrations are achieved after carbimazole administration, as compared with an equivalent amount of administered methimazole,[17] a 5-mg dose of carbimazole is equal approximately to administration of 3 mg of methimazole.[1] The difference in serum concentrations achieved likely explains why dosage recommendations differ for these two medications.[23]

Recommended initial dosing of carbimazole for hyperthyroid cats is 5 mg PO q8h. Unlike methimazole, for which treatment q12h is effective, carbimazole is more efficacious in control of hyperthyroidism if given q8h in the initial weeks of therapy.[17] When receiving carbimazole 5 mg PO q8h, more than 90 per cent of cats have serum total T_4 concentrations within the target range within 3 to 15 days.[17] With long-term therapy, administration often can be reduced to q12h and remain effective.[1] As with methimazole, conservative initiation of therapy with carbimazole has been recommended to reduce the incidence and severity of side effects.[1] Accordingly, carbimazole could be given at a dose of 2.5 mg q12h for 1 week, followed by 5 mg q12h for 3 weeks. Further alterations in dosage are based on evaluation of serum T_4 measurements.

As with methimazole, adverse effects associated with carbimazole occur typically within the first 3 months of therapy. Similar mild side effects are observed, including vomiting, anorexia, and lethargy, in addition to mild transient lymphocytosis, eosinophilia, or leukopenia (see Table 22-1).[23,24] However, vomiting and anorexia appear to be less common with carbimazole, possibly because of the tastelessness of carbimazole compared with the bitterness of methimazole.[1] Idiosyncratic facial pruritus and pursuant excoriations have been observed with carbimazole therapy.[17,24] Unlike with methimazole therapy, however, serious adverse effects such as thrombocytopenia, agranulocytosis, hepatopathy, and positive antinuclear antibodies have not been described in cats treated with carbimazole.

Other Medical Therapies

Other medical therapies have been used, including stable iodine and radiographic contrast media (e.g., sodium or calcium ipodate, iopanoic acid), which release iodine when metabolized. Additionally, β-receptor blocking agents have been used for treatment of cardiovascular complications associated with hyperthyroidism.

Stable Iodine

Supraphysiological doses of iodide decrease the rate of thyroid hormone synthesis and release transiently, a phenomenon known as the Wolff-Chaikoff effect, and believed to be a result of inhibition of both thyroid peroxidase-catalyzed iodination and thyroglobulin endocytosis.[17] In addition to reduction of systemic thyroid hormone levels, iodide therapy also may reduce thyroid vascularity, which eases intraoperative surgical dissection.[1]

A saturated potassium iodide solution in combination with a β-antagonist such as propranolol has been used successfully for perioperative stabilization of hyperthyroid cats.[25] In the protocol found to be most effective and associated with the least amount of adverse effects, propranolol was administered (2.5 mg/cat PO q8h) starting 20 days preoperatively (day 1). The heart rate was determined each morning. If the heart rate exceeded 200 beats/minute on day 4, the dosage was increased to 5 mg/cat q8h and, if it still exceeded this rate on day 7, the dosage was increased to 7.5 mg/cat q8h. From days 11 to 20, propranolol administration was continued and, initially, 42.5 mg potassium iodate (equivalent to 25 mg free iodine) was administered PO q8h. Surgery was performed on day 21. Because of adverse effects (e.g., vomiting, anorexia), the dosage of potassium iodate was decreased to 21.25 mg (equivalent to 12.5 mg free iodine) q8h, with no further side effects noted. Although the serum T_4 concentrations decreased

significantly with this protocol, only 36 per cent of patients had normal T_4 concentrations on day 20. Serum T_3 concentration was normal in 89 per cent of cats that had an elevated concentration initially. An alternative to using potassium iodate tablets is to administer 1 to 2 drops of a saturated solution of potassium iodide (SSKI).[1] The iodine, whether pills or solution, should be placed in gelatin capsules to prevent excessive salivation.[1]

Although iodine administration has some efficacy in treating hyperthyroidism, methimazole and carbimazole have more consistent and successful results and their administration preoperatively is preferred. However, for cats that cannot tolerate methimazole or carbimazole, iodine administration for stabilization is an option. Because the effects of stable iodine therapy are inconsistent and short-lived, it is not suitable for chronic disease management.

Iodinated Radiographic Contrast Agents

Oral cholecystographic agents affect thyroid hormone metabolism in human beings by acting as potent inhibitors of type I and type II deiodinases, thereby blocking conversion of T_4 to the more biologically potent T_3.[26] In addition, iodine released during metabolism of these agents blocks secretion of thyroid hormones. Oral cholecystographic agents reduce serum T_3 concentrations rapidly in human beings, with a lesser effect on T_4,[26] and both ipodate and iopanoic acid have been used successfully for short-term management of hyperthyroidism.[27-31]

Use of oral cholecystographic agents for control of feline hyperthyroidism has been limited. In a single study, calcium ipodate was efficacious in eight of 12 spontaneously hyperthyroid cats over a 14-week period; four cats (33 per cent), however, did not respond. The initial dosage was 50 mg/cat PO q12h but was increased to 150 mg/cat (100 mg in the morning, 50 mg at night), and then 200 mg/cat daily (100 mg PO q12h) at 2-week intervals as needed to control thyroid hormone secretion and resolve the clinical signs. Only serum T_3 concentrations decreased significantly, while serum total T_4 levels remained elevated. No adverse clinical signs or hematological abnormalities attributable to ipodate treatment occurred. Similar to results seen in human beings, however, at least half of the cats that responded initially relapsed within 6 months of initiating therapy.[32] Whether all cats that respond originally would relapse is unknown, but oral cholecystographic agents are not useful for long-term treatment in at least a proportion of hyperthyroid cats. In human beings, exacerbation of hyperthyroidism may even be observed with continued use.[26] The apparent lack of significant side effects makes oral cholecystographic agents an option for short-term management as may be required for presurgical stabilization.[1,26] As more cats are treated, however, occurrence of some adverse effects will be noted.

Unfortunately, calcium ipodate and sodium ipodate are no longer available. Iopanoic acid given at the same doses has been suggested as a substitution, but no data exist regarding efficacy or adverse effects.

β-Receptor Antagonists

β-Blockers such as propranolol or atenolol have been used alone or in conjunction with antithyroid medications. Although β-receptor antagonists do not reduce thyroid hormone concentrations significantly, they are useful as adjunctive agents for controlling clinical signs and complications associated with hyperthyroidism such as tachycardia, tachyarrhythmias, hypertension, hyperdynamic myocardial activity, or hypertrophic cardiac changes in addition to polypnea and hyperexcitability.[15,17] Historically, propranolol, a nonselective β_1- and β_2-adrenoreceptor blocking agent (2.5 to 5.0 mg/cat PO q8-12h) has been used most commonly.[1] However, atenolol, a selective β_1-adrenoreceptor blocking agent, has several advantages over propranolol. It has a longer duration of activity, making dosing every 24 hours possible.[1] Atenolol typically is used at a dose of 6.25 to 12.5 mg/cat/day, but the initial dose should be low and then increased gradually to effect, that is, until heart rate is normal. Additionally, because atenolol does not block β_2 receptors, adverse effects such as bronchoconstriction do not occur.[1] Bronchoconstriction observed with propranolol use may be clinically significant in cats with concurrent airway disease such as asthma.

SURGERY

Surgical thyroidectomy has long been a common treatment for feline hyperthyroidism. Although a relatively simple procedure, thyroidectomy can cause significant intraoperative and postoperative morbidity and mortality. Cardiac and metabolic complications associated with hyperthyroidism may require presurgical medical stabilization before anesthesia and surgery (see above).

Thyroidectomy procedures have been well described elsewhere.[1,33] A decision must be made whether to perform a unilateral or bilateral procedure, because both thyroid lobes are involved in 70 to 75 per cent of cats.[1] An unaffected lobe should be atrophied because of the negative feedback effect of high circulating concentrations of thyroid hormones on pituitary TSH secretion; therefore a lobe that looks normal is still suspicious. Failure to remove the affected but grossly normal-appearing thyroid lobe can result in failure to control hyperthyroidism or, if initial control is achieved, recurrence within approximately 9 months.[34] Failure also may occur if ectopic hyperfunctioning thyroid tissue is present and not detected and removed. Performance of a nuclear scan can help determine if the disease is unilateral or bilateral and if hyperfunctioning ectopic tissue is present; however, this type of thyroid imaging typically is limited to referral institutions.

Surgery has several disadvantages. Intraoperative problems associated with thyroidectomy include anesthesia-induced complications such as cardiac arrhythmias in addition to hemorrhage associated with thyroid dissection.[33,35,36] Postoperatively, Horner's syndrome and laryngeal paralysis also have been observed.[35] The most significant life-threatening complication of thyroidectomy is severe hypocalcemia that occurs as a result of parathyroid injury, devascularization, or inadvertent removal of all parathyroid tissue secondary to bilateral thyroidectomy.[33,35,36] With bilateral procedures, care should be taken to preserve parathyroid tissue and blood flow. Hospitalization and close monitoring should be performed for 4 to 7 days postoperatively to detect biochemical and clinical signs of hypocalcemia, using treatment with calcium and vitamin D therapy if needed.[1] The incidence of complications depends largely on the expertise of the surgeon, the thoroughness of preanesthetic evaluation, and presurgical management of the patient.[1]

RADIATION THERAPY

Radioactive iodine (I^{131}) administration is an effective and safe treatment for hyperthyroidism.[37] Like stable iodine, radioactive iodine is taken up and concentrated by the thyroid gland. Beta particles are emitted, which cause necrosis and destruction of the hyperfunctioning tissue within their field of travel.[1] Because these particles do not travel more than 2 mm with an average path length of only 400 μm,[1] a benefit of radioactive iodine therapy is that local tissues, including parathyroid glands, are spared. Additionally, normal, nonadenomatous thyroid tissue will have atrophied, so radioactive iodine uptake is inhibited in these cells and normal thyroidal tissue is not destroyed. Therefore, permanent hypothyroidism rarely occurs after radioactive iodine therapy, and, if it occurs, seldom requires therapy.[38,39] Although many cats may have a lower serum T_4 concentration after radioiodine treatment, only approximately 2 per cent develop clinical and clinicopathological signs of hypothyroidism and require supplementation.[39]

Approximately 95 per cent of hyperthyroid cats achieve remission with a single dose of radioactive iodine, becoming euthyroid within 3 months of treatment.[1] Approximately 2 to 5 per cent of cats require a second treatment to be cured.[1,39] Disadvantages of radioiodine therapy include the limited available treatment facilities and the need for radiation safety knowledge and monitoring equipment. Additionally, cats must be hospitalized an average of 7 to 10 days after administration of the radioactive iodine, depending on local radiation safety guidelines. Cost may be limiting for some owners but is similar to the cost of surgery in most instances. Furthermore, over time the cost of medical therapy and the associate required rechecks also are often equivalent to the cost of radiotherapy.

Controversy has persisted regarding the need for withdrawal of antithyroid medications before radioiodine administration. Concern exists that antithyroid drugs may interfere with thyroidal ability to uptake and concentrate radioactive iodine molecules.[1] One study found recently that discontinuation of methimazole less than 5 days or 5 or more days before therapy did not affect efficacy.[40] However, a study in normal cats suggested that uptake actually may be enhanced if methimazole is withdrawn 4 to 9 days before iodine administration, presumably as a result of a "short-term rebound effect" of thyroidal tissue.[41] This latter finding could suggest that discontinuation of methimazole within this time frame before radioiodine administration may increase the risk of hypothyroidism, that is, the normal thyroidal tissue will have rebounded and uptake larger amounts of radioiodine. Indeed, a trend ($p = 0.06$) existed in hyperthyroid cats in one study that cats with the shortest period of methimazole withdrawal before receiving their radioactive iodine were most likely to become hypothyroid as judged by serum T_4 measurement.[42] The clinical significance of this tendency, however, needs to be evaluated further, because not all cats that develop subnormal serum T_4 concentrations post-radioiodine therapy need to be treated for hypothyroidism.[39]

CHEMICAL AND HEAT ABLATION

Several newer treatments aimed at destroying hyperfunctioning thyroidal tissue have been reported recently, including percutaneous ethanol injection and radiofrequency heat ablation.

Percutaneous Ultrasound-Guided Ethanol Injection

Ultrasound-guided percutaneous ethanol injection has been used successfully in human beings suffering from hyperthyroidism as well as hyperparathyroidism,[43-45] and in dogs with hyperparathyroidism.[46] Ethanol injection results in vascular thrombosis and coagulative necrosis within the treated parenchyma.[47]

Ultrasound-guided percutaneous ethanol treatment of eight hyperthyroid cats determined to have unilateral disease by hormone measurement, cervical ultrasound, and nuclear scintigraphic scan has been reported.[48] The affected thyroid lobe was visualized ultrasonographically and injected percutaneously via ultrasound-guided needle placement. Any cystic fluid present within the thyroid lobe was aspirated before treatment. A 100 per cent ethanol solution was injected, with the volume injected determined through ultrasound estimation of complete infiltration of ethanol within the thyroid lobe. All cats treated had normal total T_4 concentrations within 48 hours of treatment and remained euthyroid for at least 18 months after treatment.[48] Two of the eight cats treated had a change in voice, possibly because of unilateral laryngeal paralysis secondary to ethanol extravasation into cervical tissues and damage to the recurrent laryngeal nerve.[47] Although treatment of unilateral disease appears efficacious, use of antithyroid drugs, surgery, or radioiodine may be better in the long term. In addition, ultrasound-guided percutaneous ethanol injection requires great expertise and is not readily available.

Treatment of hyperthyroid cats with confirmed bilateral disease has been less successful.[47] Bilateral thyroid gland nodules were observed ultrasonographically and confirmed as hyperfunctional via nuclear scanning. Ethanol injection of both thyroid glands during the same treatment period was performed in two cats; bilateral laryngeal paralysis and death occurred in both.[47,49] Six additional cats with bilateral disease were treated in a staged manner with the largest of the two thyroid lobes treated first.[47] Transient euthyroidism was observed in all patients, but no cat remained euthyroid for longer than approximately 6 months.[1,47] Complications observed included ipsilateral and transient Horner's syndrome, dysphonia, and laryngeal paralysis. As a result of the failure to achieve successful long-term disease control, in addition to the occurrence of life-threatening side effects, percutaneous ethanol ablation of bilateral thyroid nodules is not recommended.[47]

Percutaneous Ultrasound-Guided Radiofrequency Heat Ablation

Ultrasound-guided needle placement for heat ablation has been used in human beings to ablate small masses in hepatic, breast, and prostatic tissues[50,54] and in dogs for treatment of hyperparathyroidism.[55] Radiofrequency energy is converted to heat at the needle tip, which causes thermal necrosis of exposed tissue.[56] Tissue destruction as a result of radiofrequency treatment is believed to result in fewer complications than that seen with ethanol ablation, in part because of the greater control in application without leakage into surrounding tissues as can be observed with ethanol.[56]

Radiofrequency heat ablation therapy of nine cats with confirmed hyperthyroidism has been reported.[56] Using thyroid scintigraphy, four of the cats treated were determined to have unilateral disease and five to have bilateral thyroid

involvement. The affected thyroid lobe was treated in cats with unilateral disease, while the larger of the two lobes was treated in bilaterally affected cats. Using ultrasound guidance, an insulated needle was directed into the abnormal thyroid lobe. Unipolar radiofrequency pulses were applied, with gradual increases in energy output until the abnormal thyroidal tissue became hyperechoic ultrasonographically; hyperechogenicity is associated with the tissue necrosis caused by heat ablation.[1] Heat ablation was performed 14 times in the nine cats. Those cats undergoing more than one procedure had the additional treatment(s) performed because of either failure of the initial treatment(s) to produce euthyroidism or recurrence of hyperthyroidism.[56] Transient decreases in serum T_4 concentrations were observed within 2 days after all treatments. Euthyroidism existed for 0 to 18 months (mean, 4 months); one cat failed to become euthyroid. Hyperthyroidism recurred in all cats. Adverse effects included transient Horner's syndrome in two cats, and unilateral, nonsymptomatic laryngeal paralysis in one cat.[56]

Therefore, unipolar heat ablation is an effective short-term treatment for feline hyperthyroidism.[56] However, based on the need for multiple treatments, recurrence in all reported cases, and occurrence of Horner's syndrome and unilateral laryngeal paralysis in some cats, other safer and more effective treatments are available and may be better options. Also, as for ethanol injection, heat ablation requires great expertise and is not readily available. Ongoing evaluation of radiofrequency is assessing bipolar rather than unipolar heat ablation. Initial results suggest bipolar ablation is superior to unipolar.[1]

FUTURE DIRECTIONS OF THERAPY

Medications aimed at reducing thyroidal hormone production, surgical removal of thyroidal tissue, and radioiodine therapy are the traditional methods for treatment of hyperthyroidism. Novel tissue ablation methods such as radiowave or ethanol applications also have been attempted. Each of these methods has its own inherent advantages and disadvantages, but none, with the possible exception of radioiodine therapy, can be directed singularly to cause thyroidal cytotoxicity without risk to surrounding structures. Initial evidence suggests that somatic gene therapy could be used successfully in the future to deliver cytotoxicity specifically to thyroidal cells; however, much work must be done before this type of treatment becomes a clinical option.[57]

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Chapter 23

Goiter in Apparently Euthyroid Cats

Duncan C. Ferguson and Richard Freedman

Toxic adenomatous hyperplasia or nodular goiter in cats is considered to be one of the most, if not the most, common feline endocrinopathies. It is similar to nodular goiters in human beings with a higher frequency among the elderly. However, nonfunctional thyroid masses are being recognized more frequently in cats. Clinical data and information from retrospective studies summarized in this review suggest that thyroidal enlargement can occur in cats without evidence of overt thyroid hormonal excess. Veterinary practitioners are conducting wellness examinations more actively in aging cats and identifying the physical abnormality of goiter before its dominance and suppression of remaining normal thyroidal tissue. Rarely, a thyroid adenocarcinoma may form and lose the differentiated function of hormonogenesis and be nonfunctional; however, goiters in euthyroid cats most often apparently are caused by early stages of adenomatous hyperplasia or cystic changes.

This chapter examines retrospective studies that support the presence of a subset of apparently euthyroid cats with goiter. The issues associated with interventional management of nonfunctional thyroid nodules also are addressed. Early surgical removal of the enlarged thyroid gland(s) frequently is validated by abnormal histopathology, which suggests that with time the goiter may have become functional. Finally, this chapter also examines the current state of knowledge about the pathogenesis of goitrogenesis, focusing on new basic science and clinical information on the progression from normal thyroidal tissue to goiter. Theories on the mechanism of progression should account for the fact that iodide uptake, thyroglobulin synthesis, and iodide organification are highly differentiated cellular functions. In addition, rapid autonomous growth may be either new traits of cells generated during goitrogenesis or the result of more rapid expansion of naturally occurring cell strains with intrinsically short replication rates.

IDENTIFYING GOITER ON ROUTINE HEALTH SCREENS OF CATS

Veterinarians are presented daily with feline patients of all ages. Old cats are presented as frequently as three times per year. In my* practice, wellness consultations are scheduled once yearly. Historically, these examinations often were conducted in conjunction with scheduled immunizations. However, today veterinarians are faced with changing protocols for immunizations, especially in senior pets. A unique opportunity exists to focus more on education of cat owners about changes that occur as their pets' life cycles from one stage to the next. Veterinarians have an opportunity and an obligation to discover any health issues during these visits. Some common problems that occur in old cats include dental, cardiovascular, gastrointestinal, urological, and musculoskeletal disease. Careful history taking is important. Additional information, especially that relating to any newly discovered abnormalities, should be collected after completion of the initial physical examination.

Most hyperthyroid cats are evaluated because of specific clinical signs noticed by their owners, including weight

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loss, polyphagia, hyperexcitability, and increased vocalization. Physical findings can include tachycardia, weight loss, heart murmurs, poor hair coat, and palpable thyroid nodules. Diagnosis of hyperthyroidism usually is straightforward, because most hyperthyroid cats have elevated serum total thyroxine (TT_4) and free thyroxine (FT_4) concentrations (see Chapter 21).

However, previous reports[1-4] and clinical impressions suggest that goiter also may be present when a patient is brought to the hospital for problems not suggestive of hyperthyroidism. Therefore, in the limited time allotted for appointments in many hospitals, palpation of the thyroid gland may be overlooked during physical examination. Furthermore, for the same reason, if a goiter is identified but no clinical signs of hyperthyroidism exist, a clinician may not take the time to explain the importance of the findings to a cat's owner. An additional impediment to communication between a clinician and owner is the fact that the significance of goiter in the absence of clinical signs is not well understood.

THYROID CLINICAL ANATOMY AND PALPATION TECHNIQUE

Reports from experienced feline practitioners using careful palpation techniques indicate that more than 90 per cent of clinically hyperthyroid cats have at least one, and usually two, palpably detectable thyroid nodules. Normal thyroid lobes are not palpable because they are flat (i.e., average thickness of 2 to 3 mm) and lie ventrolateral to the trachea and dorsal to the medial borders of the sternothyroideus and sternohyoideus muscles.

Norsworthy has described a technique for palpation of feline thyroid lobes that illustrates the importance of recognizing the ability of thyroid lobes to move, and of altering the angle of a cat's head to avoid having the lobes obscured by the cervical musculature. In this approach, a cat is held in sternal recumbency with the clinician standing behind the cat. While extending the cat's neck and turning the cat's head away from the side being palpated, clinicians should palpate in the groove between the trachea and the cervical muscles with their index finger. Starting at the level of the larynx, that side of the neck should be systematically palpated ventrally down to the thoracic inlet. In general, an enlarged gland is felt as it slides quickly ("pops") away from your finger after it moves over the area. Each side of the cervical region should be carefully palpated independently, recognizing that small changes in the angle or extension of the cat's head may be necessary, just as in the procedure of jugular venipuncture. Each side should be palpated two to three times if a nodule is not felt initially, with the head position changed each time.[5]

INTERVENTIONAL THERAPY FOR EUTHYROID GOITER

We and other clinicians assume that the presence of palpable thyroid lobes suggests early changes associated with the development of hyperthyroidism.[1,2] Therefore, the question arises whether treatment should be considered when an enlarged thyroid lobe(s) is detected even if serum thyroid hormone concentrations are within reference ranges. The arguments for surgical intervention before development of overt hyperthyroidism include the following:

1. To preempt clinical hyperthyroidism. The clinical impression is that it is inevitable if the cats are not treated and followed for 1 to 2 years.
2. To minimize anesthetic risk and surgical morbidity. If surgery is performed 1 to 2 years after initial detection of the enlarged thyroid lobe(s), increased age and accompanying metabolic changes and greater gland size and vascularity may pose more problems, including a greater risk of damage to the vascular supply to the respective parathyroid glands.
3. To prevent development of weight loss, cardiac disease, and hypertension that could occur as the goiter becomes functional.
4. To document histopathological changes present in goitrous tissue.[2]

Medical therapy also can be discussed with the client to avoid progression to hyperthyroidism. Radioactive iodine therapy can be considered, but it may not be an option for some owners because of geographical and cost limitations, and the efficacy and side effects of treating cats with nonfunctional thyroid nodules are unknown. Antithyroid medications can be used (e.g., methimazole). However, the appropriate goal of such therapy is to restore euthyroidism, not cure the disease, and in a euthyroid cat, therapeutic endpoints are more difficult to establish. Also, many clients choose not to medicate their cat twice daily for the remainder of the pet's life, which could span 5 years or more.

STUDIES SUGGESTING NONFUNCTIONAL GOITERS PROGRESS TO BECOME FUNCTIONAL

Retrospective Clinical Study

Norsworthy, Adams, McElhaney, et al[1] outlined a clinical case series in which the senior author palpated and graded the sizes of both thyroid lobes from 0 (unpalpable) to 6 in 155 cats. A "1" was assigned to a lobe that was just barely palpable, and a "6" was assigned to a lobe approximately 2.5 cm or greater in length. Of the 155 cats, some reviewed retrospectively and some prospectively, 132 (85 per cent) were classified as euthyroid, and 22 (15 per cent) were classified as hyperthyroid based upon a normal and elevated serum total T_4 (TT_4) concentration, respectively. At least one enlarged lobe (score > 0) was detected in 22 of 23 (96 per cent) hyperthyroid cats and in 78 of 132 (59 per cent) euthyroid cats.[1]

Unfortunately, in this study, the selection criteria for inclusion were not evident. Although unclear, the clinician likely was aware of the clinical history and results of thyroid diagnostic testing performed before the examination. The authors concluded that the score for the largest lobe was best correlated with the serum TT_4 concentration, because all cats with a score of 4 or higher had an elevated serum TT_4 concentration and clinical signs consistent with hyperthyroidism. Five cats had elevated thyroid values and palpation scores less than 4. Three of these five cats had marginally elevated TT_4 values (52.8 to 61.8 nmol/L) and were considered hyperthyroid, which illustrates that mildly enlarged thyroidal tissue can be functional. One of the goiters in these cats was biopsied and confirmed to be a thyroid adenoma. Two of the five cats had elevated TT_4 concentrations despite a thyroid score less than 4, and

enlargement of ectopic intrathoracic thyroidal tissue was identified by technetium scanning.[1]

Prospective Clinical Study

As a follow-up to the retrospective study, the same authors followed some of the 155 cats over time. Forty of the 155 cats were examined on more than one occasion over days to years. Six of these 40 cats, all of which had an original palpation score of 0 to 2, were followed for 11 to 31 months. All developed overt clinical hyperthyroidism as judged by the authors, although the TT_4 rose above the normal range (72 nmol/L [N:13-67]) in only one cat. In 20 of the 155 cats, even with no signs of hyperthyroidism, normal TT_4 concentrations and a thyroid score of 1 to 3, the cervical mass was removed surgically. It should be noted that only five of 20 (25 per cent) of these cats had bilateral disease at the time of surgery. Thirteen of the 20 cats (65 per cent) had histopathological changes typical of hyperthyroidism, such as adenomatous change. Four cats (20 per cent) had nonproliferative changes (e.g., cysts), whereas two (10 per cent) had a parathyroid adenoma. One cat (5 per cent) had normal thyroidal tissue.[2]

Interestingly, nine cats (45 per cent) also were reported to have changes consistent with thyroiditis, which other pathologists might interpret as thymic remnants. True thyroiditis is an uncommon finding in feline thyroid glands but has been described.[6] Even though circulating immunoglobulins have been demonstrated in 34 per cent of hyperthyroid cats, they have not been shown to impact growth or function of thyroid follicular cells.[7] Because the inflammation was mainly adjacent to expanding thyroid cysts, Norsworthy, Adams, McElhaney, et al postulated a relationship between cyst formation and thyroid inflammation, and claimed to have found similar changes in healthy, euthyroid cats.[2]

Therefore, the finding of a cervical nodule in a cat with no clinical signs of hyperthyroidism may or may not be a harbinger of future hyperthyroidism. At the least, the presence of adenomatous changes in euthyroid cats was proven.

Retrospective Histopathological Study

An initial retrospective study of thyroidal tissue sections from cats seen at the University of Pennsylvania identified 26 cats with no obvious clinical or historical evidence of hyperthyroidism, normal serum TT_4 concentrations, and a histopathological diagnosis of thyroid adenomatous hyperplasia.[3] The authors concluded that adenomatous changes may occur in the absence of hyperthyroidism. Unfortunately, serum free T_4 (FT_4) concentrations, which are a more sensitive marker of the presence of hyperthyroidism,[8] were not measured (see Chapter 21). Therefore, although a percentage of the cats probably were not hyperthyroid, some of the 26 cats may have been; the number is impossible to determine.

Using histopathology, the question of the capability of a nodule or a particular cell to synthesize hormones is difficult to assess. However, assessment of the ability to synthesize thyroglobulin, the protein on which hormonogenesis takes place, is possible. Thus, pursuant to their first study, the same investigators reported on immunohistochemical staining for thyroglobulin in an effort to establish functionality of the histologically normal tissue in addition to the hyperplastic foci.

Because of negative feedback on thyroid-stimulating hormone (TSH), normal nonadenomatous thyroidal tissue in hyperthyroid cats will atrophy. Sections of normal cat thyroids used as controls showed +2 to +3 staining for thyroglobulin, whereas tissue from hyperthyroid cats showed +3 to +4 staining in the adenomatous sections but no staining in the surrounding normal, atrophied tissue. Seventeen cats had normal serum TT_4 concentrations despite having thyroid adenomatous hyperplasia. Evaluation of thyroglobulin staining verified a euthyroid state. Ten of the 17 cats had no measurable staining in the nodular area, five had small areas of +1 to +3 staining, and two had +3 staining. Most indicative of the presence of euthyroidism, all 17 cats with adenomatous hyperplasia and TT_4 concentrations in the normal range had +3 to +4 staining for thyroglobulin in the normal nonatrophied follicles, which indicates that the adenomatous areas likely were not functional because TSH was not suppressed.[4] These results are suggestive of euthyroid goiter; a similar situation occurs in chemical or iodine-deficiency goiter in which thyroglobulin synthesis can occur in excess without hormonogenesis.

Prospective Clinical and Histopathological Study

In my* private practice, a series of cats have been evaluated that had a palpable goiter detected during routine health examination. In about two thirds of these cats, a history of weight loss could be elicited, more than 33 per cent had heart murmurs, and 20 per cent were tachycardic. However, none of the cats had serum TT_4 or FT_4 concentrations above the reference range nor had serious nonthyroidal illness that could suppress the TT_4 and FT_4 concentrations. Surgery was performed to remove the enlarged thyroid lobe; no significant morbidity occurred. On histopathology, approximately 80 per cent of the cats had adenomatous hyperplasia, 15 per cent had cystic changes, and 5 per cent had an adenoma (Figures 23-1 through 23-4).[9] Interestingly, the average age of the cats was almost 2 years younger than the average age of 13 years reported by large studies.[10,11]

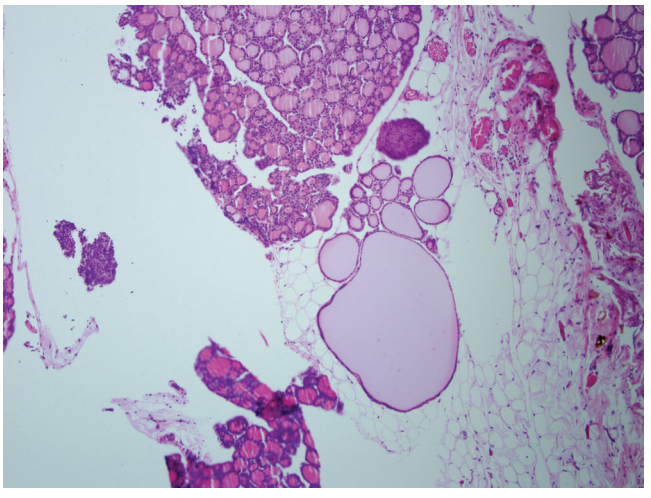
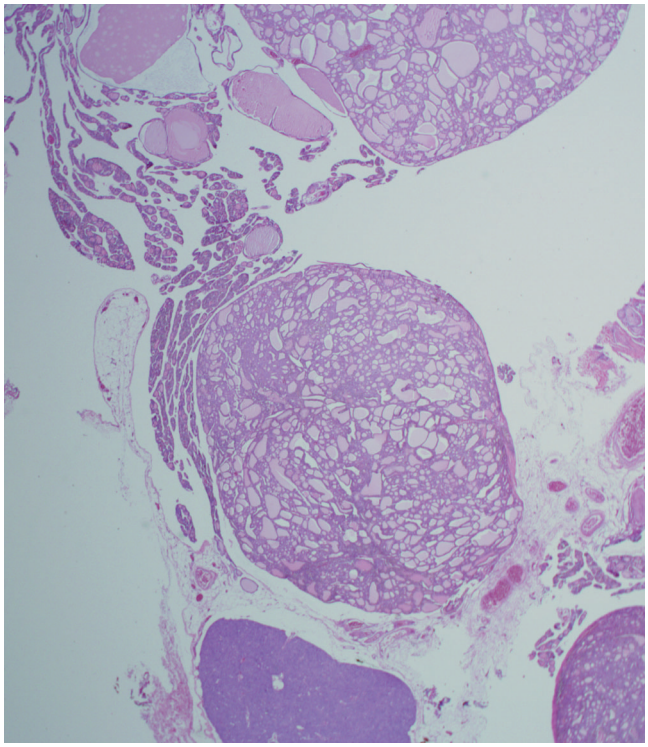
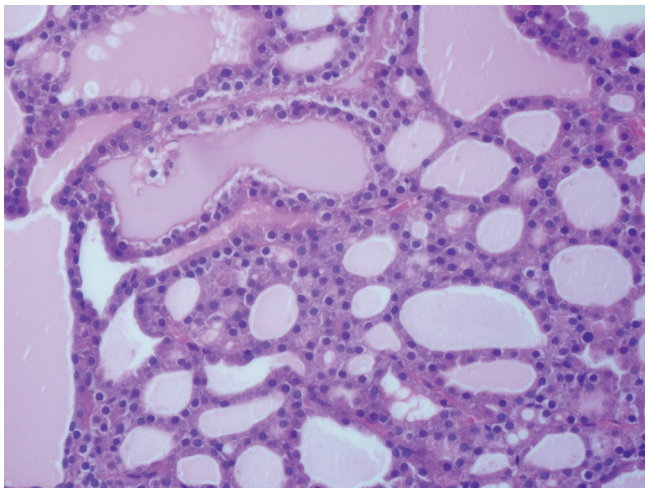


Figure 23-1. Example of normal thyroid follicles and tall cuboidal to columnar epithelium, consistent with active thyroglobulin synthesis and epithelium with follicular cysts (40× magnification).

*One of the chapter co-authors, Richard Freedman.



A



B

Figure 23-2. A and **B,** Example of nodular hyperplasia consistent with hyperthyroidism, together with follicular cysts, large Kursteiner pseudocysts (fetal parathyroid remnants), and thymic remnants. This thyroid tissue was removed from a cat with a euthyroid goiter (40× magnification).

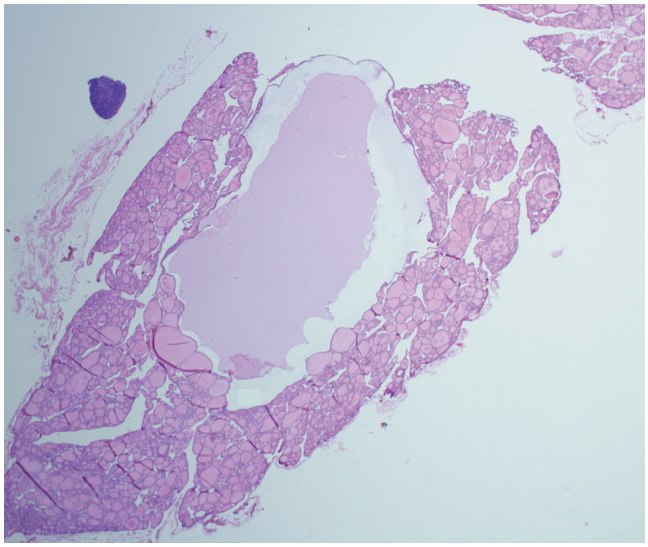


Figure 23-3. Example of nodular hyperplasia consistent with hyperthyroidism, together with follicular cysts, a large Kursteiner pseudocyst, and thymic remnants. This thyroid tissue was removed from a cat with a euthyroid goiter.

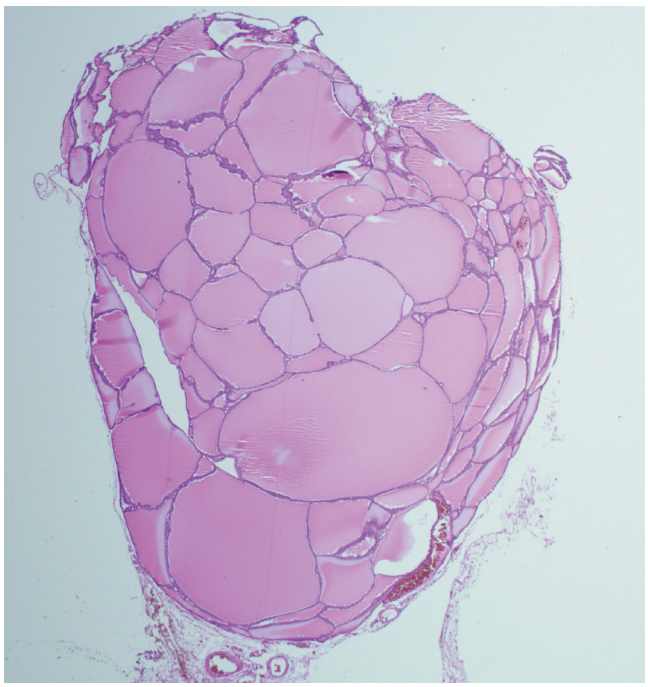


Figure 23-4. Example of nodular hyperplasia consistent with hyperthyroidism but with massive diffuse accumulation of colloid in large follicles. This thyroid tissue was removed from a cat with a euthyroid goiter.

Although Norsworthy's studies[1,2] showed that thyroid cysts may occur in glands of clinically healthy cats, cystic structures are more likely to occur when epithelial cells are dividing rapidly, which perhaps accounts for detection of goiter before autonomous hyperfunction. The finding of thyroid pathology in the majority of cats with a goiter but normal TT_4 and FT_4 concentrations suggests that serum hormone concentrations may be an insensitive indicator of the presence of disease. Indeed reexamination of the TT_4 and FT_4 concentrations in our series of cats reveals that serum FT_4 concentrations, the more sensitive marker of hyperthyroidism, was in the uppermost quintile of the normal range in almost half the cats, whereas TT_4 concentrations were not similarly elevated. Therefore, if FT_4 measurements were performed routinely and more stringent cutoff points were used for elderly cats, these "euthyroid" cats might be suspected as being biochemically hyperthyroid.

In conclusion, as in other studies, we demonstrated the presence of nonfunctional thyroid adenomas in cats. The remaining question is whether early intervention averts clinically relevant hyperthyroidism. If these early adenomatous changes

represent autonomously functioning thyroidal tissue, we believe that the tissue would continue to grow and cause clinical disease.

VAGARIES OF THYROID DIAGNOSTIC TESTS FOR EARLY OR BORDERLINE HYPERTHYROIDISM

Biochemical Testing

In addition to our findings above, other studies have shown that diagnostic tests for hyperthyroidism might be normal at the time of clinical examination of a hyperthyroid cat (see Chapter 21). In one study of hyperthyroid cats, hour-to-hour variation was found in TT_4 concentrations when sampled serially throughout the day, but the variability did not appear to account for possible misdiagnoses because serum TT_4 concentrations never fell within the reference range. However, these cats had average TT_4 concentrations double the upper limit of normal, and this study did not evaluate concentrations over multiple days.[12] In comparison, another study found that serum TT_4 and total T_3 (TT_3) concentrations can fluctuate into and out of the normal range over a period of days.[13] Reasonably a period may exist when autonomous thyroidal tissue only suppresses TSH concentrations partially, which allows some secretion from the remaining normal thyroidal tissue.

Although nonthyroidal diseases were not identifiable in the reported series of cats with euthyroid goiters, TT_4 concentrations might be depressed by undetected illness from elevated levels to concentrations within the upper half of the reference range, a situation labeled by some investigators as "occult" hyperthyroidism.[14] However, in cases of occult hyperthyroidism, FT_4 concentrations would be more likely to be elevated, with the caveat that some euthyroid sick cats may have elevated FT_4 concentrations (approximately 6 per cent)[8] (see Chapter 21).

In the future, a sensitive feline-specific TSH assay may be useful in further investigation of early changes in thyroidal function. Use of the commercially available canine TSH assay (Diagnostic Products Corp., Los Angeles, CA) to measure feline TSH in hyperthyroid cats has not provided the sensitivity necessary to clearly distinguish normal TSH concentrations from the low or undetectable concentrations expected in hyperthyroid cats.[15] Of 34 cats with chronic progressive renal disease and normal serum TT_4 concentrations, 17 were hyperthyroid as documented by T_3 suppression testing or by an elevated FT_4 concentration. All hyperthyroid cats had TSH values as measured by the canine assay at the limit of detection (0.03 ng/ml), whereas the median concentration in normal cats was 0.05 ng/ml with a range of 0.03 to 0.11 ng/ml.[15] Although the serum TSH concentrations of the two groups were statistically different, the canine TSH-specific assay would, however, not be very helpful on a case-by-case basis for confirmation of hyperthyroidism in individual cats.

Quantitative Nuclear Medicine of the Thyroid Gland

In cats with a palpable goiter but normal serum TT_4 and/or FT_4 concentrations, quantitative thyroid scintigraphy would seem to be a more sensitive method for confirmation of hyperthyroidism. With this assumption, Daniel, Sharp, Nieckarz, et al used this approach to quantify pertechnetate uptake in 43 hyperthyroid cats and 8 normal control cats.[16] The 20-minute thyroid/salivary ratio of the most intense lobe correlated best with serum TT_4 concentrations, and the authors concluded this ratio was a valuable predictor of the thyrometabolic state. However, Tomsa, Hardegger, Glaus, and Reusch[17] used the TRH stimulation test, thyroid scintigraphy, and thyroidal histopathology to evaluate 11 "study" cats with clinical suspicion of hyperthyroidism but normal serum TT_4 concentrations. Cats were categorized as normal or sick hyperthyroid on the basis of the TRH stimulation test results. Three positive control cats with elevated TT_4 concentrations also were included. All 14 cats had increased thyroid/salivary (T/S) ratios, whereas only 11 cats (eight of the 11 study cats, and the three positive controls) had demonstrable nodular hyperplasia or adenoma on histopathology. The three cats with increased uptake but no demonstrable histopathological abnormalities also had the highest TRH stimulation increment (more than 60 per cent over baseline), that is, a TRH response test result consistent with euthyroidism. The investigators concluded that scintigraphy is a sensitive method of diagnosing hyperthyroidism but specificity may be a concern. Possible explanations given for positive scintigraphy in the three cats with normal histopathology were that they were true false-positives, false-positives associated with iodine depletion, or true-positives with false-negative histopathology.[17] Therefore, these results raise the important issue of controlling for iodine repletion when establishing normal T/S pertechnetate ratios.

UPDATE ON STUDIES OF THE PATHOGENESIS OF FELINE HYPERTHYROIDISM

The time course of the functional and histopathological progression of normal feline thyrocytes to hyperfunctional adenomatous hyperplasia or adenoma is not known. However, in recent years, epidemiological and biochemical studies have led to information that suggests that environmental and/or nutritional factors play a role. However, the lack of TRH stimulation or T_3 suppression found in hyperthyroid cats, which are used as diagnostic markers of the disease, suggests that once overt hyperthyroidism is achieved by whatever means, the hyperfunctional tissues are dominant and growing and functioning autonomously.

EPIDEMIOLOGICAL STUDIES OF FELINE HYPERTHYROIDISM: POINTING THE FINGER AT ENVIRONMENTAL AND DIETARY CONSTITUENTS

With a disease that develops at such an advanced age, prospective studies of causative factors generally are not feasible. However, recent epidemiological studies have refined and strengthened earlier studies that pointed toward possible environmental and nutritional factors.

Evidence for Feline Goitrogens

In an epidemiological study of 56 cats with hyperthyroidism and 117 matched controls, Scarlett, Moise, and Rayl[18] determined an increased risk for hyperthyroidism was associated with regular treatment with flea sprays or powders (3.4-fold risk, $p = 0.03$), living strictly indoors (fourfold risk, $p = 0.05$),

and exposure to lawn herbicides, fertilizers, and pesticides (3.5-fold risk, p = 0.1). They were the first to suggest that the greater the amount of canned food in the diet, the greater the risk of hyperthyroidism (3.4-fold; p = 0.02). Siamese cats appeared to have a tenfold lower likelihood for developing the condition (p = 0.02), which suggests that genetic factors also may play a role in the development of hyperthyroidism.[18]

A more extensive case control study by Kass, Peterson, Levy, et al[19] of 379 hyperthyroid and 351 control cats found that cats fed commercially prepared canned food had an approximately twofold increase in risk of developing hyperthyroidism compared with cats that did not eat canned food. Again, a threefold increase in risk was observed among cats exposed to cat litter, and a protective effect was seen for Siamese and Himalayan cats. In contrast, the use of commercial flea products was not associated strongly with development of hyperthyroidism.[19]

In 2000, Martin, Rossing, Ryland, et al[20] reported on 100 hyperthyroid cats and 163 control cats. Neither breed nor pesticide exposure was associated with an increased risk of becoming hyperthyroid. However, cats fed fish or liver and giblets flavors of canned cat food had an increased risk of hyperthyroidism.[20] Edinboro, Scott-Moncrieff, Janovitz, et al[21] attempted to narrow the field of dietary factors with an even more extensive retrospective study that included 169,576 cats over a 20-year period, 3570 of which were hyperthyroid. From these cats, 109 hyperthyroid cats and 173 control cats were chosen for a case-control study. Type of food and type of can for canned food were studied; cans were classified as "pop-top" or requiring a can opener to open. Consumption of more than 50 per cent canned food was associated with a higher risk of developing hyperthyroidism, and the relative risk of hyperthyroidism increased with increasing length of time on this diet. In addition, cats that ate food from pop-top cans also had an elevated risk compared with those that ate canned food from cans requiring a can opener.[21]

Goitrogenic compounds in food or the environment generally reduce the efficiency of thyroid hormone synthesis by the thyroid gland, increasing TSH secretion secondarily and leading to thyroidal enlargement. Aside from iodine, most dog and cat foods contain relatively high levels of goitrogenic compounds such as phthalates.[22] Cats may be exposed to many other goitrogenic materials (e.g., resorcinol, polyphenols, polychlorinated biphenyls) either in their diets (particularly fish-containing diets) or the environment, which could contribute to the development of thyroid adenomas. Following the observation that pop-top cans were associated with a higher risk for hyperthyroidism and that these cans usually are plastic-lined, Edinboro, et al noted a previous review of data supporting an effect of plasticizers on thyroidal function.[23] In fact, the plasticizer bisphenol A (BPA) has been shown to leach from plastic containers upon sterilization and has been detected in 15 canned cat foods.[24] BPA is a known endocrine disruptor of the reproductive and thyroid axes, possibly acts as a thyroid receptor antagonist,[25] and may even influence thyroid hormone organification.[23] Even more intriguing is the fact that most polyphenolics such as BPA are metabolized by glucuronidation, a process that is particularly slow in cats.

Isoflavones inhibit 5′-deiodinase activity, and polyphenolic soy isoflavones, in particular, genistein and daidzein, have been identified in almost 60 per cent of cat foods tested; 5′-deiodinases are enzymes that convert TT_4 into the biologically active T_3. In particular, virtually all dry and semi-moist foods that contain soy protein had more than 11 μg/g of isoflavones, which, when calculated to total dietary intake, signifies exposures of 0.6 to 4.5 mg/kg of body weight, levels adequate to interfere with thyroid function.[26] Indeed, in a crossover feeding study of 18 healthy experimental cats, cats fed a soy-containing diet had higher TT_4 and FT_4 concentrations than cats fed a soy-free diet, whereas TT_3 concentrations were the same. The authors noted that although TT_4 and FT_4 were increased only by an average of 8 per cent and 14 per cent respectively, four of 18 cats on soy-containing diets had FT_4 concentrations above the normal range compared with only one on the soy-free diet. Genistein was found in the urine of 10 of the 18 cats even before entrance into the study, which suggests that cats may have persistent body burdens of these isoflavones.[27]

Three mechanisms may account for an increased serum FT_4 concentration in cats fed soy-containing diets: (1) Inhibition of 5′-deiodinase could lead to diminished intrapituitary T_3 concentrations and therefore increased TSH secretion. As a result thyroidal T_4 production would increase, causing elevated TT_4 and FT_4 concentrations, whereas peripheral 5′-deiodinase inhibition would inhibit a concomitant increase in serum TT_3 concentration. (2) Serum T_4 binding to serum carrier proteins by the isoflavones is inhibited, together with inhibition of 5′-deiodinase. In fact, isoflavones are known to be potent inhibitors of the binding of thyroid hormones by transthyretin (TTR or thyroid binding prealbumin). Decreased binding would increase the amount of unbound T_4, that is, increase FT_4. (3) Direct thyroidal effect enhances the efficiency of T_4 production, leading to an increased TT_4 and FT_4. Inhibition of 5′-deiodinase would, again, lead to a normal circulating TT_3 level.[28]

Therefore, if nutritional/environmental factors that have dose-, time- and perhaps age-dependent cumulative effects on feline thyroidal function exist, feline nodular growth, particularly under chronic stimulation of TSH, feasibly may evolve over time. As a result, clinicians may recognize glandular enlargement before the nodules become functional.

THEORIES DEBUNKED OR LOSING FAVOR

Dietary Iodine Content

Although evidence exists that both in vivo and in vitro iodide could be a moderator of thyroidal growth and function, iodide excess or deficiency does not explain the autonomous nature of hyperthyroidism in cats. A daily variation in dietary iodine content may result in wide swings of iodine that would, over a long time, contribute to development of thyroidal disorders.

Several studies have examined the iodine content of cat foods in an attempt to implicate iodine as a cause of feline hyperthyroidism. Although perhaps not relevant to the causation of hyperthyroidism, one study in cats with preexisting hyperthyroidism showed that low iodine diets had little effect on thyroidal function tests.[29] On the other hand, the iodine content of several American cat foods is up to 10 times the recommended level,[30,31] and all cat foods sampled in a study of toxic constituents in pet foods contained added iodine in synthetic form.[22] The foods exceeding the recommended iodine level were products derived from liver, kidney, beef by-products, and marine fish. Canned food production has seen a trend toward more gourmet products that contain more animal tissue (often marine fish). Dietary

iodide may have a modulatory effect on circulating thyroid hormone concentrations, but seems less likely to be a primary cause of adenomatous changes.

Circulating Antibodies Causing Hyperfunction

Increased thyroidal growth and function in feline hyperthyroidism may be due to circulating stimulatory factors, perhaps immunoglobulins. Despite the evidence that thyroidal tissues from affected cats are autonomous in growth and function, increased titers of serum thyroid growth-stimulating immunoglobulins (TGIs) have been studied in cats with hyperthyroidism to determine if an immune-related mechanism exists. These autoantibodies, which promote thyroidal growth but do not stimulate thyroidal hormone secretion, have been reported in human patients with toxic nodular goiter, in addition to patients with Graves' disease, Hashimoto's thyroiditis, and euthyroid goiter.[16,31]

A recent study reported the cloning, sequencing, and transient expression of the feline TSH receptor (TSHR). To test the possibility that hyperthyroid cats develop antibodies that stimulate the TSHR and therefore increase thyroidal function, the cloned feline TSHR was expressed in a mammalian cell line and exposed to sera or purified immunoglobulins from hyperthyroid cats, and adenylate cyclase activity was measured. Because activated TSHR normally increase adenylate cyclase activity and no stimulation of this enzyme was observed, the investigators concluded that no evidence existed for the presence of circulating thyroid stimulation factors as a mechanism underlying the pathogenesis of feline hyperthyroidism.[32]

Presence of Feline Thyroiditis

As mentioned earlier, the presence of lymphocytic thyroiditis has been reported in cats; if present, thyroiditis might be interpreted as a precursor to immune-mediated thyroidal damage and/or stimulation. However, some pathologists interpret the histopathological changes not as thyroiditis but as thymic remnants, and the preponderance of the studies of serum or serum immunoglobulins has not been supportive of the presence of a feline equivalent of Graves' disease (antibodies directed against the TSHR, see above) or autoimmune thyroiditis, which usually is associated with eventual hypothyroidism in most species. Despite very early reports of possible serum antithyroglobulin antibodies (TgAA) and antinuclear antibody (ANA) from hyperthyroid cats,[6] thyroiditis is not believed to be a common finding in cats and certainly is not associated with the development of hyperfunctional thyroidal tissue.

PATHOGENESIS OF FELINE HYPERTHYROIDISM: WHEN DOES HYPERFUNCTIONALITY OCCUR? IS IT INEVITABLE?

Key observations about goitrous tissue from hyperthyroid cats are summarized in the following section.[33]

Benign Functional Tissue

Feline hyperthyroidism is caused by excessive concentrations of circulating thyroid hormones produced by hyperplastic, benign adenomatous and, rarely, malignant thyroid glands. Until the last 25 years, few references to pathological abnormalities of feline thyroid glands had been reported. In a review of approximately 500 cats per year necropsied at The Animal Medical Center from 1970 to 1984, an average of less than two cats per year were found to have gross evidence of thyroidal enlargement of any etiology in the period before 1977, when the first cat with hyperthyroidism was diagnosed at that institution. Since 1977, both the prevalence of thyroidal pathological abnormalities and the associated clinical state of hyperthyroidism have been detected at a markedly increasing frequency, with the present incidence potentially as high as about one in 50 cats examined.[21] Functional thyroid adenomatous hyperplasia, involving one or both thyroid lobes, is the pathological abnormality associated with 97 to 99 per cent of the cases of feline hyperthyroidism. Distinction between normal and hyperplastic tissue may be difficult because the transition is likely to be gradual.[29]

Autonomy of Thyroid Function

Little is known about the pathogenesis of autonomy in thyroid nodules. Several possible mechanisms include increased sensitivity to TSH, development of sensitivity to normally inactive factors or hormones, or release from an inhibitory factor (e.g., inhibition of inhibitory G protein, see below). Excessive hormone production by thyroidal tissue evolves.

Autonomy of Thyroid Growth

The normal thyroid gland contains subpopulations of follicular cells with a constitutively high growth potential. In a thyroid gland destined to become goitrous, a fraction of these cells may replicate autonomously. Once these rapidly dividing cells are present in sufficient numbers, they may grow in the absence of any further extrathyroidal stimulation. The development of follicular cell adenomas may be the result of the preferential growth of cell clones with reduced sensitivity to a factor(s) that inhibits growth.

Propensity for Bilateral Disease

A striking feature of feline hyperthyroidism is that enlargement of both lobes occurs in approximately 70 per cent of cases. Because no physical connection exists between feline thyroid lobes, researchers have postulated that circulating factors (e.g., immunoglobulins), nutritional factors (e.g., dietary iodine), or environmental factors (e.g., toxins or goitrogens) may interact to cause thyroidal pathology in cats.

Cellular Heterogeneity

Thyroid tumor cells in most species are heterogeneous with respect to growth potential and function. Within one thyroid lobe and even within a thyroid follicle, individual thyroidal epithelial cells differ in proliferative potential. In fact, in every functional characteristic studied so far in primary culture of cells from feline goiters and in cell lines from such tissues, responses have been heterogeneous. This stepwise activation of new sets of cells enables the thyroid to adapt its activity in an economical way to changing demands.[33,34]

IS ADENOMATOUS THYROIDAL TISSUE ONE STEP AWAY FROM NORMALCY?

G Protein Mutations, but No TSH Receptor Mutations

Normally in thyroid cells, the TSHR interacts with a heterotrimeric G protein, which has three subunits, α, β, and γ. When TSH is bound to its receptor, the TSHR is activated and will bind to the G protein, in turn activating it. G proteins can be either stimulatory (G_s) or inhibitory (G_i) with respect to activity of the enzyme adenylate cyclase. In other words, if an activated receptor binds G_s, adenylate cyclase activity increases, whereas if the receptor binds G_i, enzymatic activity decreases. Augmented adenylate cyclase activity leads to mitogenesis and hormone production.

In human patients with benign adenomatous goiter, mutations in the TSHR gene have been identified as possible causes of autonomous function. Mutations of codons 480 to 640 of the TSHR gene, the segment that encodes the transmembrane region of the receptor, often have been implicated as causing constitutive activation of growth and function; for example, mutation of this area allows the TSHR to stimulate production of thyroid hormones even when no TSH is bound to the receptor. The TSHR gene from feline hyperthyroid nodules has been sequenced, but no mutations were found in this part of the gene.[35] Similarly, no abnormalities were found within codons 66 to 530 of the TSHR gene in 10 hyperthyroid cats, which encodes the extracellular part of the receptor as well. In four cats, however, a mutation was found in the gene for the α-subunit of the G_s protein, which suggests that mutations in this gene might play a role in the etiopathogenesis of feline hyperthyroidism.[36]

Two recent reports demonstrated that tissue from hyperthyroid cats had reduced quantity of G_i proteins. Thyroidal tissue was removed surgically from eight hyperthyroid cats and four age-matched euthyroid cats. A diagnosis of hyperthyroidism was made initially on the basis of clinical signs and an increase in serum TT_4 concentrations and was confirmed by histopathological analysis of thyroidal tissue. Western immunoblotting was performed to assess expression of G_s and G_i proteins. No difference was found in amounts of G_s between hyperthyroid and control cats. However, hyperthyroid cats had a significant decrease (62 per cent) in the α-subunit of G_i. These results may indicate that G_i normally may play a role in the inhibition of growth and differentiation of feline thyroid glands, and decreased amounts of G_i could lead to cell growth and hyperthyroidism. A subsequent study demonstrated the $G_{i\alpha 2}$ subtype was suppressed in feline thyroid adenomas.[37,38]

Proto-oncogenes are found in normal cells and overexpression possibly could be an initiating alteration in a normal cell, eventually leading to autonomous function. An immunohistochemical study of formalin-fixed, paraffin-embedded thyroid glands from 18 hyperthyroid and 14 euthyroid cats evaluated overexpression of the products of oncogenes c-ras and bcl2, and the tumor suppressor gene p53. Of note, all sections from areas of nodular follicular hyperplasia/adenoma stained positively for overexpression of the c-ras protein (also known as p21) using a mouse monoclonal antihuman pan-ras antibody; thyroid and parathyroid glands from euthyroid cats did not stain positively. The regions that stained most intensely positive in the hyperthyroid cats were in luminal cells of the follicles. Staining for either bcl2 or p53 was undetectable in any of the cats.[39] The trigger for stimulating the increase in expression of p21 remains to be elucidated, but likely either TSH or a factor acting similarly stimulates differentiated cell growth. Because c-ras and the p21 protein it encodes interact with G proteins, these studies on G_i, c-ras, and p21 elucidate the findings of earlier studies in cultured cell lines from hyperthyroid cats, which suggested some abnormality existed between the TSHR and adenylate cyclase.[40-42]

Comparison to Progression in Human Hyperthyroidism

What is known about the natural course of development of autonomous thyroid hyperfunctional nodules in human beings, and how might that compare with what veterinarians are seeing with preventive health protocols for elderly cats? Bauch, in a 1998 review, noted that 90 per cent of human patients with hyperfunctional thyroidal tissue had a euthyroid goiter for a prolonged period of time before becoming hyperthyroid.[43] After the age of 40, the risk of hyperthyroidism increases gradually, and hyperthyroidism also can occur in the absence of goiter. For physicians, the most sensitive evidence of functional thyroid autonomy is quantitative evaluation of pertechnetate uptake. Baseline TSH concentrations or TRH-stimulated TSH concentrations are considered 2.5 times less sensitive.[43] In human beings, where present, iodine deficiency leads to the development of a diffuse homogeneous goiter and increases the frequency of nodules and adenomas. However, even for human patients, the presence of iodine deficiency does not explain the generation and growth of thyroid nodules, or their functional heterogeneity. Also, a small subgroup of toxic adenomas have been associated with mutations of the TSHR or the gene for the α-subunit of G_s, providing the only molecular explanation for the development of adenomatous goiter.[34,43,44]

CONCLUSION

Functional and nonfunctional thyroid nodules are more common with age in human beings. The reviewed studies demonstrate that both in cats dying of other causes at a university hospital in addition to cats detected with goiter on physical examination in a private practice, elevations of TT_4 and FT_4 concentrations may be mild or nonexistent. The adenomatous tissue may be nonfunctional or borderline hyperfunctional, and an increased incidence of cystic follicles may be contributing to the detection of euthyroid goiter. Preemptive surgery may be considered appropriate for some patients, given the high likelihood of development of thyroid functional autonomy and overt hyperthyroidism.

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Chapter 24

Diagnostic Usefulness of and Clinical Syndromes Associated with Reproductive Hormones

Brenda Griffin

Reproductive hormone assays have a number of clinical applications in feline practice. In this chapter, recently published information regarding the diagnostic usefulness of luteinizing hormone (LH) and relaxin is presented in context with their clinical applications. In addition, the diagnostic use of hormone challenge studies and clinical findings to diagnose cryptorchidism and ovarian remnant syndrome is reviewed.

DISTINGUISHING BETWEEN SEXUALLY INTACT AND ALTERED CATS

Tomcats: Cryptorchid, Monorchid, or Neutered?

Definition and Clinical Relevance

Cryptorchidism is a congenital defect in which one or both of the testes do not descend into the scrotum at the appropriate time. The testicles may be retained anywhere along their normal path of descent from the abdomen and may be located in the subcutaneous tissue of the groin between the inguinal ring and scrotum, in the inguinal ring, or in the abdomen. Monorchidism is defined as the development and presence of only a single testicle, regardless of location, and is exceedingly rare in cats. For this reason, cats presenting with only one scrotal testicle should be considered cryptorchid until proven otherwise.[1]

Retained testes do not produce spermatozoa but do produce testosterone.[1] Affected cats may or may not be fertile depending on whether a scrotal testis is present, but in any case are likely to develop androgen-dependent behaviors including urine spraying. Urine spraying in general is the most common behavioral problem reported in cats and is a common reason for relinquishment of pet cats by their owners.[2,3] Although many causes of spraying exist, cryptorchidism should be considered as a differential diagnosis in a male cat, especially when an adolescent or young adult cat presents for spraying. (This is the expected time for a tomcat to begin experiencing the behavioral effects of testosterone.) Although relatively uncommon, this cause of spraying is associated with an excellent prognosis because removal of the retained testicle(s) most often results in resolution of spraying. Even with a history of previous castration, the possibility of cryptorchidism should not be discounted, because conceivably the surgeon may have removed only one testicle in a unilaterally cryptorchid cat and mistaken the cat for a monorchid.

Incidence and Pathogenesis

The incidence of cryptorchidism is low. In one study of 1345 cats, only 23 (1.7 per cent) were cryptorchid.[4] Two cats (0.002 per cent) in the same population had true monorchidism; spermatic cords and vessels were traced to a blunt terminus and no testicle was found. Compared with mixed breed and other purebred cats, the prevalence of cryptorchidism is significantly higher in Persian cats. In one study, 29 per cent (five of 17) of Persian cats were cryptorchid compared with 1.4 per cent (18 of 1328) of non-Persian cats.[4] Similar Persian breed predilection (20 per cent) was documented in a separate retrospective study of 50 cryptorchid cats.[5]

Most cases of cryptorchidism are unilateral (78 per cent and 90 per cent in two large retrospective studies).[4,5] Significant differences have not been noted in the locations of unilaterally retained testicles in comparison of inguinal with abdominal and left with right sides.[4,5] Testicles may be located within the inguinal ring itself.[5] In cases of bilateral cryptorchidism, testicles have been reported more commonly to be located intraabdominally,[4] but unilateral and bilateral subcutaneous inguinal testicles occur.[5,6]

In cats, the testicles usually are present in the scrotum at birth, and they are readily palpable at the time of the first

veterinary visit (usually at 6 to 8 weeks of age).[7] Although delayed or late testicular descent may be relatively common in dogs (up to 6 months), this generally is not the case in cats. The exact factors that are involved in regulation of testicular descent are unknown, but normal hypothalamic-pituitary-gonadal axis function and testicular secretion of both androgenic and non-androgenic hormones appear to be necessary.[1] Administration of gonadotrophic hormones induces early testicular descent in some species; however, protocols for administration of gonadotropin releasing hormone (GnRH) or human chorionic gonadotropin (hCG) have not been evaluated scientifically in cats, are not recommended, and should never be attempted if the inguinal rings have closed.

In dogs, cryptorchidism is an inherited disorder. This has not been proven in cats; however, the predisposition in the Persian breed suggests that it may be hereditary. Whereas the development of Sertoli cell tumors is relatively common in dogs with retained testicles and an increased risk for spermatic cord torsion is present, these conditions are exceedingly rare in cats and do not pose significant concern.[1]

History and Clinical Signs

Bilaterally cryptorchid cats and unilaterally cryptorchid cats (in which surgical removal of the scrotal testicle has been performed) may be mistaken as neutered cats because of the absence of scrotal testes. These cats may be presented for sexual behaviors including spraying, fighting, and mounting, or for the presence of a strong urine odor.[4] Owners should be questioned carefully regarding the administration of exogenous hormones, including anabolic steroids, which could be metabolized into progesterone and testosterone and result in male behaviors.[8]

Diagnosis

Demonstration of penile spines and/or an increase in serum testosterone concentration after administration of hCG or GnRH may be used for diagnosis of retained testicle(s) in cats.[9]

Clinical Evaluation

PHYSICAL EXAMINATION. A complete physical examination should be performed, including careful inspection of the penis and palpation of the inguinal area. Penile spines are reliable external indicators of the presence of testosterone in male cats and are present in both unilaterally and bilaterally cryptorchid cats. Penile spines begin to appear in kittens as early as 12 weeks of age and are obvious by 6 months of age.[10] They regress within 6 weeks after castration, and the mucosal surface of the penis becomes flat and smooth. The presence of penile spines may be considered diagnostic for the presence of elevated serum testosterone, which is due to the presence of a testicle in 99 per cent of cases[5,9,11] (Figure 24-1); a rare possibility to consider would be the existence of a testosterone-secreting adrenal tumor.

When compared with scrotal testicles, retained testicles generally are grossly smaller[12] (Figure 24-2). Testicles located in the inguinal region frequently are difficult to feel and may not be readily palpable because of the large inguinal fat pad in many cats.[5] Furthermore, irregular deposits of fat may be mistaken for retained testicle.[4]

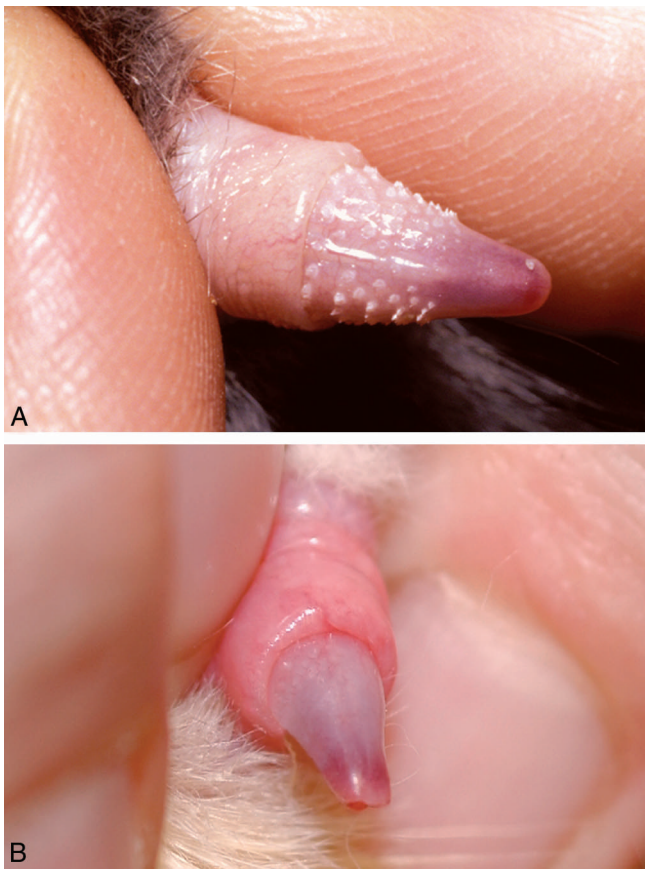

Figure 24-1. A, Examination of the penis is a valuable means of diagnosing cryptorchidism in tomcats because the presence of penile spines is a reliable external indicator of testosterone production. **B,** Within a few weeks of castration, penile spines atrophy and the penile mucosa becomes smooth and flat in appearance.

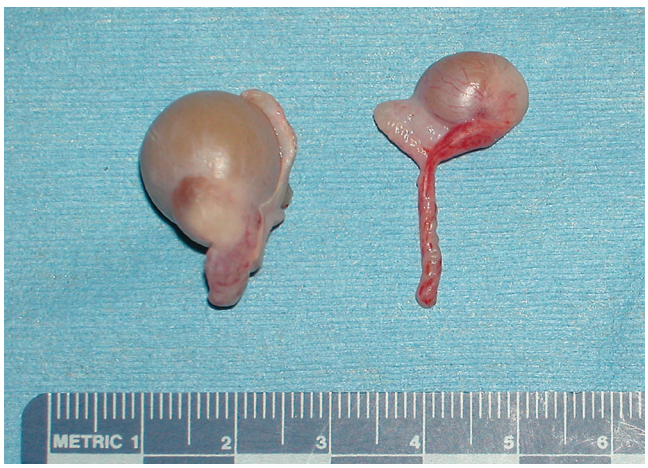

Figure 24-2. Comparison of scrotal testicle *(left)* and retained testicle *(right)* from a cryptorchid tomcat. Retained testicles generally are smaller than scrotal testicles. The retained testicle pictured here was removed from the inguinal ring, and palpation was not possible through the large inguinal fat pad.

In addition to development of penile spines, other androgen-dependent physical changes occur as cats mature to puberty. These include secondary sex characteristics such as the formation of jowls, widening of the neck, and thickening of the skin (Figure 24-3). Although most tomcats do not develop distinct

Figure 24-3. Comparison of physical features of a neutered male cat *(left)* and an intact tomcat *(right)*. Note the thick neck and the presence of large jowls in the tomcat.

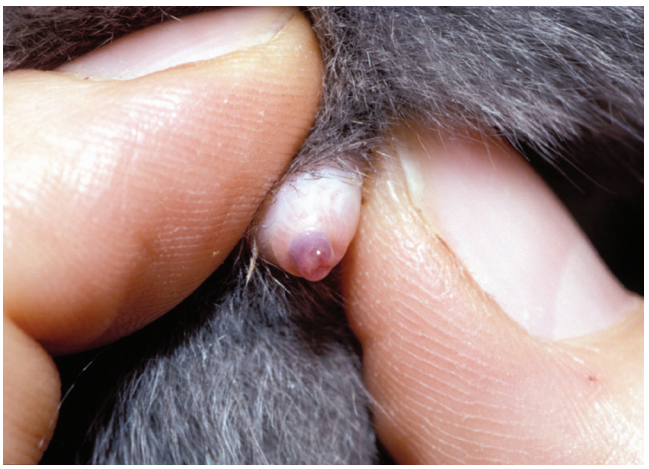

Figure 24-4. The balanopreputial fold of this neutered male cat remains intact, preventing complete extrusion of the penis. Presence of the balanopreputial fold in a postpubertal male is indicative of previous castration.

jowls before 2 years of age, their skin may appear "tougher" subjectively or more difficult to puncture with a hypodermic needle.

In kittens, the balanopreputial fold connects the penis to the prepuce and prevents full penile extrusion. Its dissolution is an androgen-dependent event that occurs as tomcats mature.[11] Tomcats are neutered routinely before puberty (which occurs typically between 8 and 13 months of age) to prevent the development of undesired male behaviors. In many tomcats neutered before puberty, the balanopreputial fold remains intact and complete penile extrusion is not possible.[13] The presence of an intact balanopreputial fold suggests the cat has been neutered (Figure 24-4).

Failure of the balanopreputial fold to regress because of neutering is not believed clinically significant, although it can be more difficult to exteriorize the penis for catheterization in the event the patient requires a urinary catheter. Numerous studies have evaluated urethral size, function, and health in neutered cats.[13-18] Neither urethral diameters nor dynamic urethral function, as judged by contrast retrograde urethrograms and urethral pressure profiles, differ significantly in neutered cats and intact cats regardless of age of neuter.[13-16] In addition, the incidence of urethral obstruction and lower urinary tract disease is not affected by age at neutering.[17,18]

Diagnostic Imaging

Retained testicles may be visualized on ultrasonographic examination of the abdomen and inguinal area, but this usually is not necessary for diagnosis. Plain radiography is unrewarding because of the small size and nondistinct radiodensity of the testes.

Hormonal Evaluation

Hormonal evaluation is the most definitive diagnostic test for differentiation of bilaterally cryptorchid and neutered animals but may not be necessary. If the history suggests testosterone secretion and penile spines are present, measurement of serum testosterone concentration will not add further information. A single resting sample with detectable testosterone concentrations means a source of testosterone exists. However, intact cats secrete testosterone in an episodic, pulsatile fashion throughout the day and resting serum concentrations range from nondetectable to greater than 80 nmol/L.[11] Therefore a single resting sample with a nondetectable serum testosterone concentration does not rule out the presence of a testicle. If a baseline sample has no detectable testosterone, a hormone stimulation test should be performed. Stimulation of maximal testosterone secretion can be accomplished in cats by the administration of hCG or GnRH. Baseline serum samples should be collected before injection of either 100 IU hCG IM or 50 µg GnRH SQ. Additional serum samples should be collected 4 hours or 1 hour post injection, respectively. A twofold to fourfold increase in serum testosterone is indicative of the presence of a testis.[1,9,11]

Treatment and Prognosis

Affected cats should be neutered. If an inguinal location of the testicles is suspected based on palpation, a midline or paramedian incision, followed by dissection deep to the inguinal fat pad, allows visualization of the subcutaneous area extending to the external inguinal ring. Once the testicle is exposed, the spermatic cord can be ligated and transected, which allows removal. Most intraabdominal testicles are located adjacent to the urinary bladder; therefore a caudal ventral midline incision is recommended. If the testicle is not identified readily, the incision may be extended cranially as necessary to allow location of the ductus deferens as they cross the ureters. The ductus deferens then may be traced to and from their respective internal inguinal rings to locate the ipsilateral testicle.[4] The use of a spay hook to retrieve an abdominal testicle is not recommended because of the risk of damaging or avulsing the ureters.[4,5] If the testicle is not located intraabdominally or is not readily palpable in the inguinal region, gentle traction on the abdominal portion of the spermatic cord can help to locate the testicle, and unnecessary dissection of the inguinal fat can be avoided.[5] Submission of the testicle for histopathology is recommended to confirm its identity, particularly if substantial atrophy is present. The prognosis for removal and recovery is excellent. Typically, male characteristics regress within a few weeks of removal of the testicle.

Figure 24-5. Cropping of the tip of the ear is performed frequently at the time of spay/neuter of free-roaming cats and serves as an identifying symbol for a sterilized cat.

Figure 24-6. Comparison of the body condition between a spayed female cat *(left)* and a reproductively intact queen *(right)*. Differences in body condition are common because metabolic rate decreases significantly after ovariohysterectomy of cats.

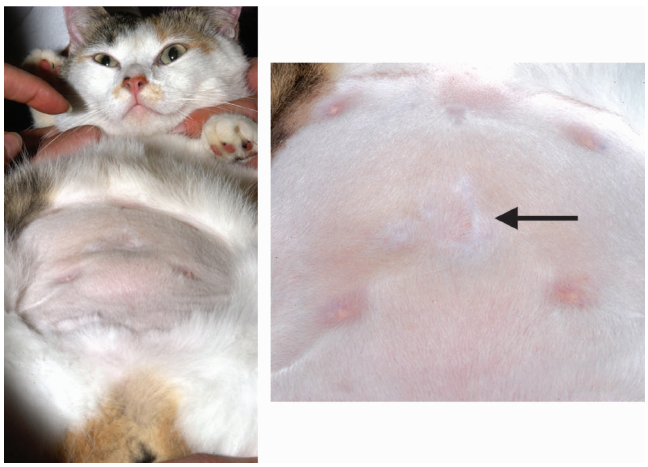

Figure 24-7. The shaved abdomen of a spayed cat. Careful inspection of the mammary glands may be helpful in distinguishing reproductively intact and spayed queens because the mammary glands of spayed cats generally are underdeveloped or atrophic. Note the presence of a "spay scar" *(arrow)*.

Queens: Reproductively Intact or Spayed?

Clinical Relevance

Accurate identification of queens that have been spayed represents a longstanding and sometimes frustrating clinical dilemma. Cats with unknown histories are presented commonly to veterinarians and animal shelters for determination of reproductive status. Various methods of identification have been used to identify surgically sterilized cats, including application of special tattoos, application of tattoo paste in the surgical incision to "mark" the surgical scar, ear cropping (removal of an ear tip, Figure 24-5), and implantation of microchips. Unfortunately, none of these methods are uniformly widespread in their use. Furthermore, evidence of an abdominal incision from previous ovariohysterectomy may be lacking, particularly if the cat was spayed at a very young age or if a flank approach was used. In many instances, cats undergo unnecessary anesthesia and surgery, only to reveal that previous ovariohysterectomy has been performed. This translates into unnecessary trauma for cats, expense for owners, and frustration for practitioners.

Clinical Evaluation

A complete physical examination should be performed. The queen's overall body condition should be noted. After spaying, metabolic rate decreases significantly and a tendency towards obesity occurs.[19,20] If the cat is overweight, a clinical suspicion that she has been spayed previously is warranted (Figure 24-6).

If a cat will cooperate, the ventral abdomen should be shaved from the umbilicus to the pubis, and the skin of the midline should be inspected carefully for the presence of a scar. In my experience, palpation alone is not a reliable indicator of the presence of a spay scar. Some intact queens have a prominent linea alba that may be mistaken for a scar. Spayed queens frequently have scars that are not readily palpable yet may be visualized once the overlying hair is removed. The inguinal area also is a common location for tattoos, which are visualized more readily once the hair is removed.

The mammary glands also should be inspected carefully. Spayed queens typically have atrophied mammary glands and very small teats subjectively, compared with the well-developed glands and prominent teats of intact queens (Figure 24-7). The pinnae should be examined for the presence of tattoos or cropping, and the patient should be scanned for the presence of a microchip. If a microchip exists, it can be used to track the cat's ownership and yield an identity and medical history.

Owners should be questioned carefully regarding behavioral signs of estrus. Most cats experience winter anestrus[21]; therefore, time of year should be considered in assessment of the presence of estrus signs. Owners may confuse normal affiliative or greeting behaviors such as cheek-rubbing or tail-waving with signs of estrus. Lordosis and treading usually can be induced in estrual queens by stroking the queen's back or dorsal rump. This can be done during the course of an examination to help verify the presence of behavioral signs of estrus. When the presence of behavioral estrus is questionable, vaginal cytology can be performed to confirm estrus if necessary.

If reproductive status cannot be determined based on physical examination, hormonal evaluation is recommended before consideration of exploratory surgery. Alternatively, owners may elect to wait and see if signs of behavioral estrus appear. Given the prolific reproductive rates of cats, the high incidence of unintentional litters and the tremendous numbers of homeless cats,[22] the latter cannot be recommended.

Figure 24-8. The Synbiotics Corporation ICG Status-LH Ovulation Timing Kit may be used to distinguish reproductively intact and spayed dogs and cats. This test is simple to use and requires only three drops of serum or plasma.

Whenever possible, definitive determination of reproductive status should be made.

Hormonal Evaluation

Tests for measuring serum concentrations of LH may be used to distinguish spayed and sexually intact animals.[23] In reproductively intact cats, the normal sequence of endocrinological events is such that LH concentrations remain at low basal concentrations, except for brief periods when ovulation induction occurs in estrual queens and GnRH stimulates LH release. After this sudden spike, LH returns to basal concentrations in less than 24 hours.[24] Negative feedback control of LH results from ovarian estradiol secretion and maintains LH at basal concentrations. When a cat is spayed, this negative feedback control is removed, and LH concentrations remain increased indefinitely.

A recent study evaluated the ability of a commercially available canine LH assay (ICG Status-LH™ canine ovulation timing test, Synbiotics Corp., San Diego, CA, Figure 24-8) to distinguish between ovariectomized and sexually intact queens. This is a semiquantitative immunochromogenic assay using gold-conjugated LH antibodies. A positive result occurs when a visual line develops indicating that the LH concentration in the sample is greater than 1 ng/mL. The kit was developed for use in dogs and is useful in distinguishing spayed from reproductively intact bitches.[23]

In a study of 50 cats (24 ovariohysterectomized and 26 sexually intact queens), all ovariohysterectomized queens tested positive and 24 of 26 sexually intact queens tested negative for LH.[25] Based on these results, the sensitivity of the ICG Status-LH Assay (the likelihood of a positive result in a spayed cat) was determined to be 100 per cent. The specificity of the test (the likelihood of a negative result in a sexually intact queen) was determined to be 92 per cent. Samples from more than 150 additional cats collected in all seasons of the year have yielded similar results.[26] In other words, all spayed cats tested positive, but if the test is negative, an 8 per cent chance still exists that the cat has been spayed. Thus the ICG Status-LH Assay appears to be a reliable and noninvasive means of determining if a queen needs to be spayed. Results always should be interpreted in relation to physical findings, and repeat testing may be of benefit in cases in which false-positive results are suspected.

Ovarian Remnant Syndrome (ORS)

Definition and Pathogenesis

ORS is defined commonly as the presence of functional ovarian tissue accompanied by signs of estrus in a female cat after routine ovariohysterectomy.[27-30] Ovarian tissue that remains after surgery may be functional immediately postoperatively, or it may continue to develop and become functional over weeks to years. In either case, estradiol production results and the cat may exhibit estrous behavior. Although extraovarian production of estradiol has not been reported in cats, estrogen secretion by the adrenal glands has been reported to cause signs of estrus in some species.[27,28] Some authors have suggested that estrogen secretion in cats with ORS may not be the result of ovarian remnants in all cases, but instead may be a result of adrenocortical production.[7,31]

Certainly, the presence of ovarian tissue as a cause of hyperestrogenemia is far more common than adrenal production; however, it is not always the result of "surgeon's error."[32,33] The presence of an ovarian remnant or remnants in a cat may be due to failure to remove all of a normal ovary at ovariohysterectomy (OHE); the presence of an "accessory ovary" that is not detected at the time of OHE; or ovarian tissue that revascularizes after being dropped back into the abdomen inadvertently after removal during OHE.[30] Failure to remove ovarian tissue completely during OHE has been attributed to improper surgical technique including poor clamp placement or lack of adequate visualization.[27,28] In one retrospective study of 29 cats with ORS, only nine of 29 (31 per cent) of the cats had been spayed by recent veterinary graduates (graduates of less than 5 years).[29] This implies that the surgeon's experience does not affect the occurrence of ORS and may suggest that the presence of extraovarian tissue is not uncommon. In fact, the presence of anomalous ovarian tissue (an "accessory ovary" in the proper ligament) has been reported in cats.[29] The presence of an "accessory ovary" may be the result of partial or complete separation of a portion of normal ovary during development.[34] Removal of the normal ovaries during routine OHE may lead to development of the previously atrophic accessory ovary and ultimately result in ORS. Indeed, hypertrophy of remaining ovarian tissue has been shown to occur after unilateral or partial ovariectomy in cats.[34]

Two studies have provided strong evidence for the theory that some cases of ORS may result from ovarian tissue being dropped into the abdominal cavity inadvertently during a spay, with subsequent revascularization of the tissue as it attaches to the omentum or other peritoneal structure. In one study, the cortices of excised ovaries in four cats were implanted into the peritoneum of the abdominal wall.[35] Two of the cats showed behavioral estrus postoperatively, and active ovarian tissue was found in all four cats via laparotomy 12 weeks later. A recent study evaluated whether or not free, autologous feline ovarian tissue can become viable and active in the abdominal cavity after OHE.[36] In this study, nine queens were ovariohysterectomized, but before closure of the abdomen, a major portion of one ovary was sutured loosely to the mesentery using nonabsorbable material. After 6 months, the remnants were retrieved

and submitted for histopathology. One remnant was free in the omentum and was determined to be nonviable based on histopathology. However, eight of nine remnants were found grossly adhered to the omentum, the lateral abdominal wall, or both. In these eight cats, ovarian tissue was viable, which illustrates that implantation is not required for ovarian remnants to survive and that the omentum provides a suitable environment for ovarian tissue to revascularize and become active.

Although reimplantation is possible, retrospective studies of ORS in cats do not support that it is a frequent occurrence, because ovarian remnants almost always are recovered at the site of the right or left pedicle or both. In one study of 29 cases of ORS in cats, only one ovarian remnant was associated with a nonpedicle location, whereas 14 cats had ovarian tissue in both the right and left pedicles, five had tissue in the left pedicle only, five had tissue in the right pedicle only, and four cats had no location reported.[29] In a report of 10 cats with ORS, all remnants were located at the pedicle, with nine of 10 on the right side.[37] In a report of 11 cats, remnants were located at the pedicle in all cats, with most on the right side and some bilaterally.[27] The right side may be a more common site of an ovarian remnant if surgeon's error is the cause, because the right ovary is more cranial and potentially more difficult to exteriorize and/or visualize during surgery.

History and Clinical Signs

ORS usually occurs in healthy cats after OHE, generally is not associated with ovarian or uterine pathology, and happens more often in cats than dogs.[27,29] Clinical signs include manifestations of behavioral estrus. Owners may note vocalization, rubbing, and "friendly" behavior, which progresses to rolling. Many queens stretch and squirm in lateral recumbency, opening and closing their paws. Additionally, they crouch and assume a lordosis stance frequently while treading in place with their hind limbs and deflecting their tail laterally (Figure 24-9). Stroking the queen's back or dorsal rump during estrus may induce this stance.

Under the influence of estrogen, a queen's vulva becomes slightly edematous and hyperemic but remains so small and well covered by hair that close inspection is required to identify changes. Vulvar discharge is scant and rarely observed because of the fastidious grooming habits of queens.[21] Queens with ORS attract tomcats and may permit copulation, but pregnancy cannot result from mating. Owners should be questioned carefully regarding possible administration of exogenous hormones (such as diethylstilbestrol) that could account for clinical signs of estrus.

Onset of signs may occur at any time from a few days to many years following OHE.[27,29] Normal interestrous intervals of 1 to 3 weeks may be seen, or several months may lapse between periods of behavioral estrus. Age at OHE does not seem to be a factor in development of ORS, and no breed predispositions have been reported.[29] Although rare, behavioral signs of pseudopregnancy also may occur in cats with ORS after ovulation, which may be induced by either copulatory or noncopulatory stimulation.[30]

Diagnosis

Differential diagnoses include other causes of clinical signs that mimic estrus: vaginitis, vaginal neoplasia, lower urinary tract disease, or catnip ingestion. Diagnosis of feline ORS is based on a combination of clinical signs, history, vaginal cytology, hormonal data, and exploratory laparotomy.

In cases in which the history and clinical signs are consistent with ORS, vaginal cytology should be performed when behavioral signs of estrus are present.[27,28,30] In general, the use of vaginal cytology as a bioassay for feline estrogen is more accurate than a single serum sample. Vaginal cytological changes in estrual queens tend to be more subtle than those of dogs but usually include an increase in cornified vaginal epithelial cells and clearing of normal background mucus (Figure 24-10). However, because behavioral estrus frequently persists beyond hormonal estrus, missing these cytological changes is possible.[21] Likewise, a single serum estradiol concentration may or may not be indicative of follicular activity. During estrus in cats, estradiol concentrations rise sharply from basal concentrations to more than 20 pg/ml before returning rapidly to basal concentrations in as few as 48 hours.[21] Although a single blood sample with a high estradiol concentration provides a diagnosis of ORS, missing estradiol elevation is possible when only a single serum sample is assayed.

Hormone challenge or response tests also may be used to confirm the presence of ovarian tissue.[28,30,37] The administration of a gonadotropin (hCG 250 IU IM) mimics the LH surge and

Figure 24-9. An estrual queen exhibits a typical display of lordosis and tail deflection.

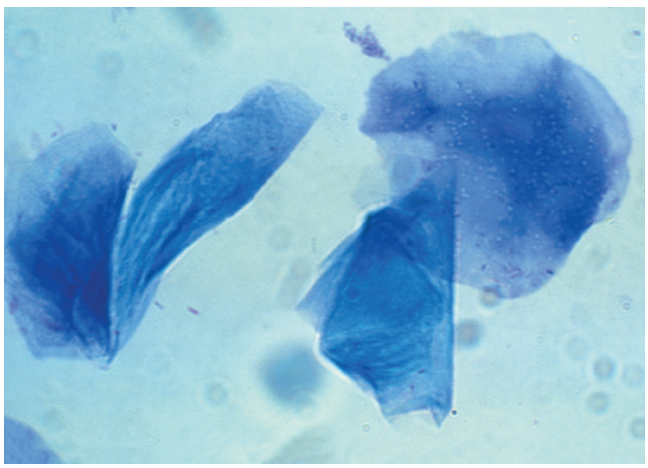

Figure 24-10. Vaginal cytology of an estrual queen reveals a predominance of cornified epithelial cells with only scant amounts of background mucus.

causes ovarian follicles to ovulate, luteinize, and secrete progesterone. In a study of 10 cats with ORS, this method induced ovulation successfully and aided diagnosis in all cases.[37] An alternative protocol is to administer GnRH (25 µg IM), which stimulates endogenous LH release.[28,30] With either protocol for ovulation induction, the hormone should be administered during behavioral estrus, and serum progesterone should be measured 1 to 3 weeks later. Serum progesterone concentrations will be greater than 2 ng/ml at that time, if ovulation was induced.[21]

Ultrasound has not been reported to be a useful diagnostic tool in the diagnosis of ORS. It is difficult for even the most skilled operator to identify ovarian structures in sexually intact animals, and the fact that the ovarian remnants usually are small precludes successful use of this technique. Exploratory surgery is the final diagnostic option, and in almost all, if not all, situations will be therapeutic as well.[27,28,30] A logical assumption is that a commercially available LH test may be useful in the diagnosis of ORS, although this has not been reported to my knowledge. Just as in the case of a sexually intact female cat, LH should be undetectable in cats with ORS. For more information on the use of this test, see the previous section of this chapter.

Treatment and Prognosis

Surgical removal of the remnant(s) is the treatment of choice (Figure 24-11). Performing surgery during behavioral estrus may be helpful because the presence of follicular structures and an increase in vascularity may make the remnant(s) easier to locate. Similarly, surgery may be performed after medical induction of ovulation because the development of corpora lutea may make the remnant(s) more readily visible. Surgical exploratory should be performed 2 to 4 weeks following ovulation induction as verified by a serum progesterone concentration of greater than 2 ng/ml.[27,30]

Each side of the abdomen should be explored completely beginning at the region of the ovarian pedicles, including the caudal poles of the kidneys. Residual ovarian tissue is located most commonly in the region of the ovarian pedicles and frequently may be bilateral. Ovarian or other suspicious tissue should be excised carefully and submitted for histopathological examination. If ovarian tissue cannot be identified at surgery, removal of the granulation tissue at each ovarian pedicle is advised.[28] Histology of the remnant and cessation of signs postoperatively confirm the diagnosis. If surgery does not resolve the signs, referral to a surgical specialist may be indicated. Many cats that are later treated successfully with surgery have undergone previous negative exploratory laparotomies.[27,28] The long-term prognosis for this condition usually is excellent.

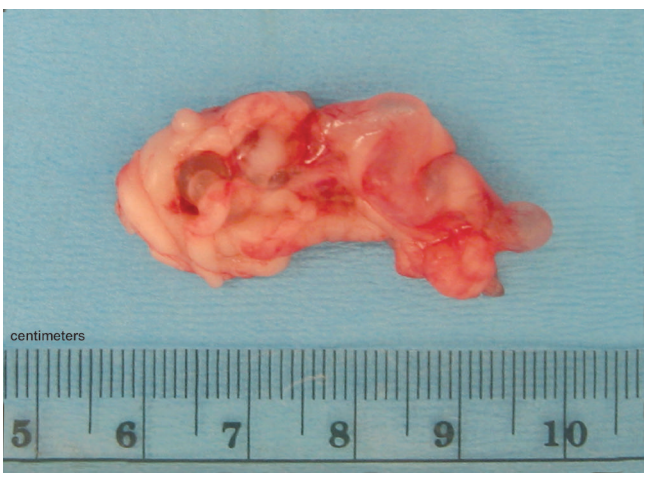

Figure 24-11. Large, cystic ovarian remnant from a cat with intermittent signs of behavioral estrus. Remnants are located most commonly in the region of the ovarian pedicles and frequently are bilateral.

Medical treatment for ORS generally is not recommended. Progestogens, such as megestrol acetate (Ovaban, Schering-Plough, Union, NJ), have been used for estrus suppression in cats but can induce diabetes mellitus, severe mammary hyperplasia or neoplasia, and adrenocortical atrophy.[21] One suggestion is that administration of prednisolone (2.2 mg/kg PO q24h for 5 days, then tapered by halving the dose every 5 days) results in permanent cessation of signs of estrus within 3 to 5 days, presumably by suppression of the adrenal axis.[7,31] If exploratory surgery is negative or if the owner declines surgical exploratory, this is a viable treatment option. However, the owner should be warned that signs might recur.

I treated one cat in this manner.[38] In this case, the cat experienced regular cyclic estrous behavior with concurrent vaginal epithelial cornification for approximately 2 to 3 months before treatment with oral prednisone. Signs ceased within days of treatment, recurring once several weeks later after a stressful move with the owner, then ceased again shortly after instituting a 3-week course of oral prednisone therapy. The cat has remained clinically normal with no signs of estrus behavior for nearly 4 years at the time of this writing.

Some owners may decline surgery. Prednisone/prednisolone therapy can be tried in these cats. If unsuccessful at stopping estrus, owners may elect to live with the periodic displays of estrus behavior in their pets. These cats may experience an increased risk of mammary carcinoma and uterine stump pyometra. In the future, safe medical contraceptives may become available and may serve as alternatives to surgery for the treatment of ORS.

DIAGNOSING FELINE PREGNANCY

Background and Clinical Relevance

Queens are seasonally polyestrous. In the northern hemisphere, the season begins typically in January or February (after the winter solstice, as the days grow longer) and lasts until fall. On average, queens display estrous behavior every 2 weeks from February to October. Free-roaming or uncontrolled queens exhibit a bimodal incidence of pregnancy: the majority of kittens are born in mid-spring and late summer. In cats, the gestation period is 65 to 67 days on average (62 to 71 days). Gestation length is variable because of the relatively long period of sexual receptivity and the uncertainty of the time of ovulation and conception. The gestation period may be divided into three trimesters, each of approximately 3 weeks' duration.[21]

Pregnancy diagnosis is a useful clinical procedure. Cat breeders frequently seek pregnancy diagnosis of their queens, particularly those with a history of infertility. In addition, queens with unknown histories commonly are presented to veterinarians for determination of reproductive status including distinguishing intact from spayed cats (see previous section) and determination of pregnancy status. Depending on the time

Figure 24-12. Signs of pregnancy become obvious during the third trimester. Note the marked abdominal distention and mammary development in this queen.

Figure 24-13. Segmental dilation of the uterus in a cat with pyometra. Although usually associated with pregnancy, segmental uterine dilation is not always a specific finding.

of year, pregnancy may be common in sexually intact queens that have been free roaming. Owners need to be informed of a cat's status and counseled on appropriate care, including such issues as the risks associated with administration of modified live vaccines during pregnancy and performing OHE to prevent kitten births. Pregnancy diagnosis also may be required in the context of biomedical research, particularly where research involves maintenance of cats with inherited diseases or when contraceptive studies are being conducted.

Clinical Evaluation

Behavioral and physical changes may aid in pregnancy diagnosis but typically remain subtle during the first two trimesters. Many queens become increasingly docile during this period and the nipples become pinker and more erect (commonly referred to as "pinking" of the nipples). By the third trimester, behavioral and physical changes are obvious and include abdominal distension, mammary gland enlargement, excessive grooming of the mammary and perineal areas, and nesting behavior[21] (Figure 24-12).

Diagnosis of pregnancy in queens may be made by abdominal palpation of fetal vesicles, by abdominal radiography or ultrasonography, or by measurement of plasma relaxin concentrations. Palpation of a pregnant uterus per abdomen is possible as early as days 14 to 17 of gestation at which time small spherical dilations of the uterus (approximately 1 cm in diameter) may be evident. By days 21 to 25, the vesicles are prominent, usually measuring at least 2 cm in diameter, and are easiest to palpate at this time. However, because segmental dilation of the uterus also can occur with pyometra, this is not always a specific finding (Figure 24-13). After days 30 to 35, the segmental fetal dilations (at least 3 cm) become more oblong in shape and tend to become confluent, which makes palpation more difficult. The enlarged, fluid-filled uterus may be difficult to distinguish from bowel loops. Late in gestation (after day 45) fetal heads and bodies often can be distinguished, and fetal movement frequently is evident. With experience, palpation is a reliable method of pregnancy detection.[21,39]

Imaging methods used for pregnancy diagnosis include radiography and ultrasound. Calcification of fetal skeletons may occur as early as day 38 of gestation but is not a reliable finding until day 43; therefore, to ensure a diagnostic study, radiography should be performed after day 43 of gestation. Uteromegaly may be seen before this date but cannot be distinguished from pyometra or other inflammatory uterine disease. Abdominal radiographs are most useful for evaluating litter size prepartum; however, because of the potential danger of radiation exposure to developing fetuses, radiographic examination generally is not recommended.[21,39,40]

Ultrasound is a rapid, safe, and reliable method of pregnancy detection in cats.[21,39,40] Although not always reliable for determining litter size, ultrasound has the advantages of assessment of fetal viability and being able to differentiate inflammatory conditions from pregnancy. Fetal exposure to ultrasound is believed to be much safer than radiographic exposure. Ultrasonographic evidence of pregnancy may be seen as early as 11 to 16 days of gestation when embryonic vesicles appear as spherical anechoic structures, 2 mm in diameter. Fetal heartbeats are detected by day 25. The normal feline fetal heart rate averages 228 +/– 35 beats per minute.[39] For tractable queens, ultrasound is a useful tool for pregnancy diagnosis and evaluation.

Hormonal Evaluation

Relaxin is the only hormone specific to pregnancy recognized presently in cats.[41] It is a peptide hormone produced by the fetoplacental unit. Plasma concentrations increase 20 to 30 days after mating and remain elevated throughout pregnancy and for the first few days after birth (Figure 24-14). The luteotrophic effects of relaxin help to maintain pregnancy and result in relaxation or softening of the connective tissues of the pelvis. Although serum progesterone concentrations are elevated during pregnancy, they are not helpful for diagnosis because they do not differ significantly in pregnant and pseudopregnant queens. A progesterone-dominant luteal phase follows ovulation regardless of pregnancy status.[21]

Measurement of plasma relaxin concentration (Witness Relaxin, Synbiotics Corp, San Diego, CA) is a reliable method of feline pregnancy detection during and after the second trimester (Figure 24-15). In one study, all pregnant cats tested

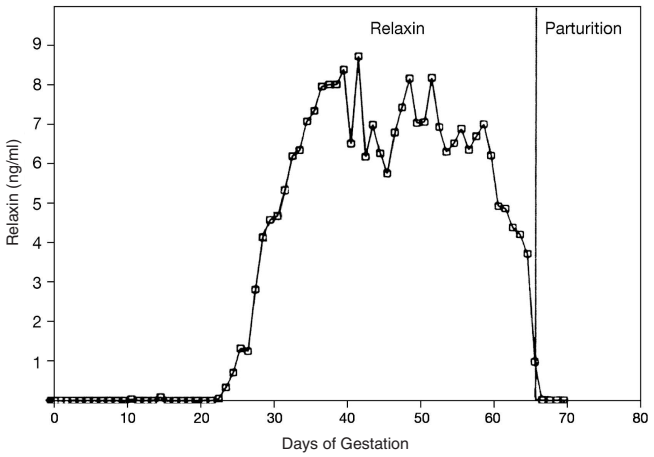

Figure 24-14. Mean concentrations of plasma relaxin in pregnant queens during gestation. (Modified from Stewart DR, Stabenfeldt GH: Relaxin activity in the pregnant cat. Biol Reprod 32:848, 1985.)

Figure 24-15. The Witness Relaxin Test Kit (Synbiotics Corp., San Diego, CA) may be used to diagnose pregnancy in cats beginning at approximately 25 days of gestation. This test is simple to use and requires only two drops of serum or plasma.

positive for relaxin (i.e., sensitivity of 100 per cent) beginning at approximately day 25 of gestation[42]; however, two of 23 nonpregnant control cats also tested positive for relaxin (i.e., specificity of 91 per cent). The two false-positive results were obtained in cats with large ovarian cysts (>2 cm), which suggests possible ovarian or luteal production of relaxin in these cats. Requiring only two drops of plasma, this test represents a noninvasive, rapid, and cost-effective method of pregnancy diagnosis. It may be of particular benefit in queens that are easily stressed by prolonged restraint as required for ultrasound examination.

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Chapter 25

Update on Feline Immunoglobulin E (IgE) and Diagnostic Recommendations for Atopy

Aiden P. Foster and Petra J. Roosje

The diagnosis of atopic dermatitis (AD) in human beings and dogs primarily is a clinical diagnosis based on the patient's history, the family history, and the distinct clinical morphology and distribution of skin lesions.[1-3] In contrast, in cats, most of the literature on what is called atopic dermatitis has focused more on a description of the existence of positive test results for the detection of allergen-specific IgE and has not elaborated on history and clinical signs. Feline atopic disease has been reported and reviewed on a number of occasions and included some details on at least 220 cats[4-20] but remains poorly understood and ill defined. The immunopathogenesis of atopic disease in cats has been presumed to be similar to that in dogs, although much of the relevant work remains to be done.

IMMUNOPATHOGENESIS

In human beings, IgE binding on epidermal Langerhans cells (LCs) is thought to facilitate allergen-specific T cell activation.[21] After capture, the allergen is processed and presented to T cells in a MHC class II restricted way.[22] The epidermis and dermis of lesional skin of cats with AD contained a significantly increased number of $CD1a^+$ cells (LCs) and MHC class II^+ cells compared with skin of healthy control animals.[23] T cells are important role players in the pathogenesis of AD, and histological examination of both human and feline AD skin reveals a predominance of $CD4^+$ T cells.[24] More specifically, an increased number of IL-4^+ T cells were demonstrated in lesional and nonlesional skin of cats with AD.[18] With double-labeling methods it was demonstrated that the IL-4 was produced primarily by T cells and not by mast cells.[25]

The exact role of connective tissue mast cells in human AD is unknown. In acute lesional AD, skin mast cells numbers are not increased, but degranulation of mast cells is observed.[26] Mast cell numbers, however, are increased in more chronic lesional AD human skin.[26]

Mast cells are predominant cells in the perivascular infiltrate in lesional skin of allergic cats.[27,28] They are present in increased numbers in lesional and nonlesional skin of AD cats compared with nonallergic cats.[29,30]

In cats, however, the numbers of mast cells and eosinophils may be increased in other nonallergic diseases, such as pemphigus foliaceus.[31] Additionally, mast cells are heterogeneous cells strongly influenced by their microenvironment. Most mast cells of healthy cats and cats with eosinophilic conditions contain chymase and tryptase.[29,32] Significantly less tryptase was observed in lesional and nonlesional skin of cats with AD, which indicates a generalized effect on mast cells.[30] As early as 1965, McCusker demonstrated that skin of cats with allergic dermatitis had a fourfold increase in mast cell numbers and histamine content.[33] Bevier and Dunston reported that mast cells showed a piecemeal type of degranulation after intracutaneous injection of allergen in allergic cats.[34]

Eosinophils can be found in increased numbers in lesional skin of allergic cats and often in the peripheral blood. The value, however, of peripheral blood eosinophilia in cats is limited, because it can be caused by several conditions including endoparasite and/or ectoparasite infestations.[35]

Although the exact content of feline eosinophil granules is not known, one study reported the presence of eosinophil granules containing major basic protein and eosinophil-associated ribonuclease, while the granule proteins have peroxidase, ribonuclease, and bactericidal activities.[35a]

Similar substances to those of human eosinophils are to be expected, because lesions analogous to human flame figures

occur in feline eosinophilic dermatoses and free granule content has been demonstrated.[36,37] The development of the atopy patch test (APT) has proven to be a valuable tool in elucidating the disease process in human beings. The APT bypasses the problem of conflicting results that occur because of differences in chronicity of the lesions of AD patients.

An APT was developed in cats in an attempt to study the allergic inflammation process. In a small study, three of six cats with AD showed erythematous skin reactions to topically applied aeroallergens, in contrast to healthy control cats and negative control sites that did not show any reaction. A significantly increased number of IL-4$^+$, CD4$^+$, CD3$^+$, MHC class II$^+$ and CD1a$^+$ cells was found in one AD cat with positive APT reactions. Five out of six AD cats had significantly increased IL-4$^+$ T cell numbers at 24 and/or 48 hours.[38] Further investigations are necessary to assess the significance of this finding. However, in line with this observation are the studies of the expression of mRNA for chemokines in the lesional skin of cats with eosinophilic plaques. The expression of mRNA for the CC-group chemokines termed thymus and activation-regulated chemokine (TARC) and regulated upon activation, normal T-cell expressed, and presumably secreted factor (RANTES) was higher by RT-PCR in lesional skin compared with nonlesional skin of these cats and in control skin of a healthy cat.[39,40] Chemokines are regarded as highly important factors in the recruitment and activation of inflammatory cells in a variety of allergic diseases.[41] RANTES is associated with chemoattraction of cells including eosinophils, whereas TARC is expressed selectively on Th2 cells but not on Th1 cells; therefore, these findings on patch testing and the detection of chemokines support the theory of a Th2-driven reaction.[42]

FELINE IMMUNOGLOBULIN E

Immunoglobulin E (IgE) is the primary antibody involved in the initiation of immediate allergic responses[43] and plays an important role in parasitic infections.[44,45] Although such allergic responses may involve passive binding of IgE to mast cells and basophils via the high affinity IgE receptor (FcεRI), accumulating evidence proves that IgE may regulate its own receptor expression and modulate immune responses via the FcεRI on other cell types.[46] The interaction between IgE antibodies and the FcεRI provides a focus for much research that may enable a better understanding of IgE-mediated diseases. This interaction has been studied at the crystal structure level and shows, for example, that the IgE molecule is bent when bound to its receptor.[47-49] Although a great deal is known about IgE in human beings and many other species, the cat has remained somewhat elusive in terms of establishing a role for IgE in allergic conditions.

Passive cutaneous reactions have been used extensively in a variety of species to establish the presence of reaginic antibody, now usually considered to be IgE antibodies. A sensitization period of 1 to 3 days is preferred for the demonstration of IgE, whereas a period of 4 to 16 hours could be associated with an IgG-based reaction.[50] After intradermal injection of sera and a period of sensitization, the recipient is challenged by either intravenous antigen for a passive cutaneous anaphylaxis (PCA) or intradermally for a Prausnitz-Küstner (P-K) test. The ability of the cat to respond to antigens with hypersensitive reactions has been recorded.[51-54] The presence of an antibody analogous to IgE was suspected from those studies using intradermal tests and PCA reactions, with a 4-hour to 5-hour interval between intradermal injection of cat serum and the intravenous injection of the relevant antigen. Walton, Parish, and Coombs[55] reported a case of allergic dermatitis and enteritis in a cat associated with the ingestion of cow's milk. The passive transfer of serum from the cat gave a positive PCA reaction in one of eight cats. The recipients received intradermal injections of serum from the affected cat and were challenged 75 minutes to 22 hours later with intravenous cow's milk or lactalbumin and Geigy blue dye. Positive results occurred after 1¼ hours with undiluted serum and a 1:5 serial dilution.

A variety of studies have used sera from cats infested with parasites to demonstrate the presence of a heat-labile serum antibody that has characteristics consistent with an IgE isotype. Weisbroth, et al[56] and Powell, et al[57] studied the response of cats to infestation with the ear mite *Otodectes cynotis* by PCA, with use of passive serum transfer from infested cats to either recipient cats or guinea pigs. The serum from cats with active mite infestations contained an antibody that was positive in these tests and was sensitive to heat treatment at 56° C and to 2-mercaptoethanol treatment. The cats were challenged after either 4 or 72 hours with positive results; guinea pigs were challenged after a 4-hour sensitization period with positive results. Evans blue and a prepared *O. cynotis* antigen were administered intravenously.

DeBoer, et al[58] reported on cats infected with *Toxocara canis* as a source of IgE. Using immunoaffinity chromatography, cat serum was incubated with monoclonal anti-canine IgE antibody bound on discs and the putative feline IgE molecule was eluted. This eluted product was studied using gel electrophoresis with SDS-PAGE, in which a protein with a similar molecular weight to canine IgE was identified. In addition, feline bladder strips were sensitized with infected feline serum and stimulated with monoclonal anti-canine IgE antibodies, with consequent contraction and histamine release. The presence of a reaginic antibody was supported further by reverse cutaneous anaphylaxis reactions with polyclonal and monoclonal anticanine IgE reagents in a cat; the reagents were injected intradermally into the recipient cat. Baldwin, De Medeiros, and Denham[59] studied the immune response of cats infected repeatedly with the filarial nematode *Brugia pahangi* by PCA (a model for *Wuchereria bancrofti* infection in human patients that may lead to obstruction of the lymphatics and "elephantiasis"). Positive reactions were seen after a 48-hour or 72-hour sensitization period with *B. pahangi*–soluble somatic adult antigen and Evans blue dye. This reaction was heat-sensitive at 56° C for 1 hour. The positive reactions were associated with those cats in which the adult worm was killed. Thus it was concluded that IgE may be important in the immune response to adult worms in the lymphatic system. In another study, PCA and P-K heat stabile antibodies were presumed to give positive test reactions after a sensitization period of 24 hours using sera samples from cats with eosinophilic plaques and miliary dermatitis; this differs from other studies.[60] A later study using P-K tests described IgE-mediated reactions (nonheated serum) and IgG-mediated reactions (heated serum) in cats with atopic dermatitis and healthy cats.[61]

In further studies, serum derived from a *Brugia*-infected cat gave positive PCA reactions in recipient cats and pigs, using an *Ascaris suum* extract after 4 and 72 hours of sensitization. Heat inactivation of the PCA reaction was achieved by heating serum to 56° C for 1 to 4 hours. Gel filtration of the serum revealed

a pattern of PCA-positive fractions similar to that observed in other species. Attempts to purify the PCA-positive sera fractions using superose gel filtration and ion exchange chromatography by fast protein liquid chromatography (FPLC) were unsuccessful. Affinity chromatography of PCA-positive material by FPLC on protein A demonstrated two bound peaks, the second of which was PCA-positive and eluted as a single peak by ion exchange chromatography. The PCA-positive fractions from gel filtration did not bind to protein G. The protein A, PCA-positive peak provided partially purified reaginic antibody for further study.[62] The PCA-positive fractions were further characterized by ELISA analysis, SDS-polyacrylamide gel electrophoresis, and Western blotting. The protein A bound peak was found to contain large quantities of IgG and small quantities of IgM, and it was not possible to separate a protein with characteristics of an IgE antibody.[62]

Further evidence for feline IgE comes from studies with cats immunized with *Toxocara cati* and dinitrophenylated ascaris antigen. Heat-labile antibody was detected by homologous P-K tests and antigen-specific ELISA. Antisera were raised to the antibody, and this gave positive reversed cutaneous anaphylaxis reactions and neutralized P-K tests.[63,64] In cats with skin disease, deemed to be atopic, the measurement of antigen-specific IgE was made using polyclonal antisera by ELISA, by P-K test, and by IDT. The results were compared with two control groups of normal healthy pet cats with no skin disease and healthy laboratory cats. Allergen-specific IgE (and IgG) antibodies were detected in atopic and normal pet cats with significantly lower concentrations in laboratory-reared cats. Serum IgE antibodies were not correlated with IDT in the atopic cats. An additional group of cats was immunized with *Dermatophagoides farinae* antigens. In the immunized cats, serum IgE antibodies were not correlated with either IDT or P-K tests. A positive P-K test usually was correlated with a positive IDT. Such results lend support to the concept of heterogeneity of IgE molecules.[65,66]

Mosquito-Bite Hypersensitivity

A distinct cutaneous disease associated with mosquito bites has helped to focus interest in the concept of the pathogenesis of eosinophilic dermatoses, particularly the eosinophilic granuloma complex (EGC), being associated with cutaneous penetration of a wide variety of antigens that may incite the formation of a granuloma. The EGC generally is considered to be a cutaneous reaction that also may be observed with inflammatory responses to environmental and food allergens.[67] In one study of six cats with various manifestations of EGC, the cats made significant cutaneous T-cell responses to the Fel d I allergen applied with a skin blister technique, which suggests its potential use as an autoallergen.[68]

A seasonal pruritic dermatitis in cats has been described secondary to mosquito bites in the United States, Australia, New Zealand, and Japan and may occur in other areas (reviewed by Mueller[69]). Allowing mosquitoes to feed on the nasal skin has reproduced the lesions in cats. The cutaneous signs of mosquito-bite hypersensitivity include papulocrustous dermatitis that affects the nose, muzzle, pinnae, preauricular region, flexor carpi, and junction of the footpad and haired skin. These lesions may progress to erosions and are associated with depigmentation. The footpads of affected cats may be ulcerated, swollen, and hypopigmented (Figures 25-1 through 25-3).

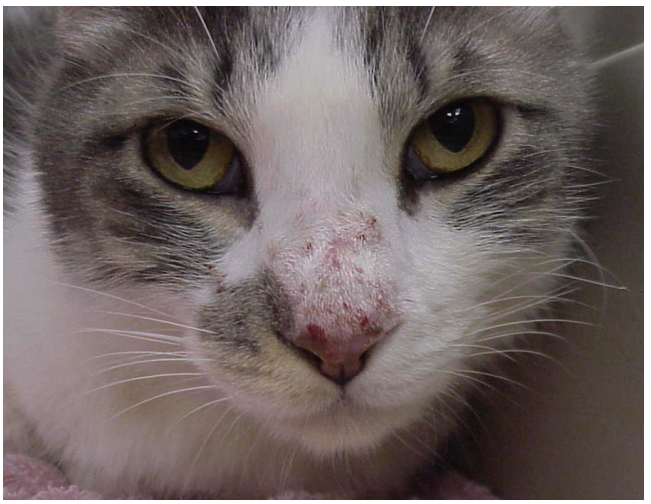

Figure 25-1. Papulocrustous lesions on the bridge of the nose of a cat with mosquito-bite hypersensitivity. (Courtesy Dr. Alice Wolf, Texas A&M University.)

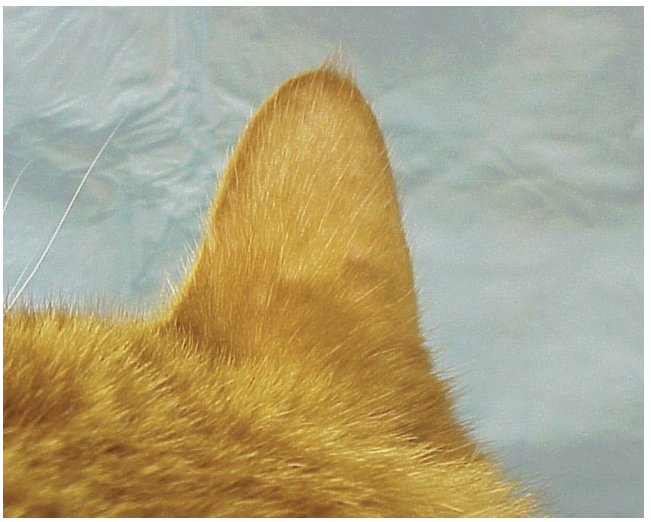

Figure 25-2. Papulonodular lesions on the skin of the external pinna of a cat with mosquito-bite hypersensitivity. (Courtesy Dr. John August, Texas A&M University.)

Differential diagnoses to consider include allergic skin disease, notably flea-bite hypersensitivity, food allergy, atopic disease, drug reaction, pemphigus foliaceus, discoid lupus erythematosus, actinic dermatitis, and squamous cell carcinoma. Cats should be kept in an insect-free environment. Cats protected by insect screening have shown resolution of signs within 7 days. The response to glucocorticoids usually is rapid and dramatic.

A peripheral eosinophilia and marked peripheral lymphadenopathy may be observed. Histopathological findings may include an intraepidermal eosinophilic infiltrate, micropustule formation, focal epidermal necrosis, serocellular crusting, spongiosis, eosinophilic cellulitis, and palisading eosinophilic granuloma. These changes confirm that this syndrome is a variant of the EGC. In some cases, eosinophilic furunculosis also may be present, which is not a typical feature of EGC.

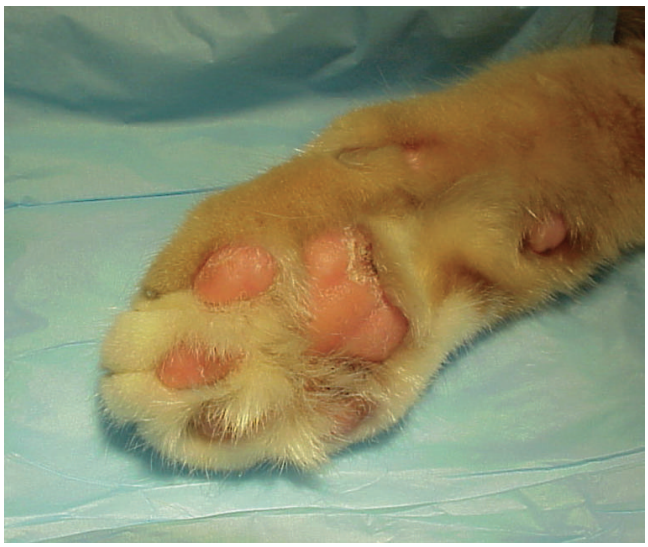

Figure 25-3. Scales and crusts at the junction of nonhaired skin on the footpad and haired skin of a cat with mosquito-bite hypersensitivity. (Courtesy Dr. John August, Texas A&M University.)

The term collagenolysis has not been used here to describe the histological features of EGC. Areas of collagen degeneration/lysis may represent the coating of collagen fibers with eosinophil granules and degradation products[70]; such areas also have been termed flame follicles. On ultrastructural examination, these areas reveal collagen fibers that are disrupted, but the individual collagen fibrils are not damaged; furthermore evidence exists of eosinophil granule release around the collagen in two ways, including cytolysis and piecemeal degranulation, admixed with epithelioid macrophages and multinucleated cells.[36,70]

The role of feline reaginic antibodies in this disease is supported strongly in a Japanese study of cats with cutaneous mosquito-bite reactions. Reaginic antibodies were demonstrated in the skin by positive reactions to mosquito-bite exposure, intradermal testing, and Prausnitz-Küstner tests.[71]

Immunoglobulin E and Cytokines in Atopy

The small quantities of IgE antibody present in serum have made the isolation and purification of IgE by conventional chromatographic techniques very difficult. The development of anti-IgE reagents to measure feline IgE can be facilitated by cloning and expression of DNA sequences encoding the constant region of the feline Cε gene. A preliminary study of the cat Cε gene (IgE heavy chain gene) used a PCR technique and peripheral blood cells from a cat infected with the nematode *B. pahangi*. Degenerate primers were designed based on the known DNA sequences for sheep, human, and mouse Cε genes. A nested PCR technique was employed, and the DNA sequence derived was 667 base pairs in size and appeared to be consistent with the second and third domains and part of the first domain of the Cε gene.[72]

A feline splenic cDNA library was screened with a ^{32}P-labeled cDNA probe encoding the canine IgE epsilon heavy chain subunit. Patel, et al[73] reported the isolation of canine IgE from a genomic bacteriophage library prepared from liver tissue using a human IgE probe. The complete canine epsilon-chain cDNA was cloned and sequenced. That study formed the basis for the production of a labeled probe used for isolating feline IgE. A cDNA sequence of 1614 nucleotides encoding the complete feline IgE heavy chain and a portion of a variable region was identified. A search of the GenBank database revealed an identity of 82 per cent at the nucleotide level and 76 per cent at the amino acid level between the feline epsilon heavy chain sequence and the canine homologue. In a separate parallel study, feline genomic DNA, isolated from whole feline embryo cells, was subjected to polymerase chain reaction (PCR) amplification using primers based on known partial genomic DNA sequences for the feline Cε gene.[72] After removal of an intron from the 683 bp PCR product, the coding sequence yielded a product of 506 bp. The DNA sequence of this PCR clone differed by a single nucleotide from the cDNA clone. This difference is silent, and therefore the proteins encoded by the two sequences are identical over the regions cloned and sequenced. Phylogenetic analysis of the constant regions of nine immunoglobulin epsilon genes revealed that the feline cDNA was most similar to the canine homologue.[74] An identical, albeit partial, feline Cε gene sequence also has been cloned by Griot-Wenk, et al.[75]

The feline Cε sequence shares close homology with other species considering that the Cε gene appears to have a high rate of evolution compared to the other immunoglobulin heavy chains.[76] The similarity of the CH3 domain sequences between species may be due to the fact that the high affinity FcεRI receptor found on mast cells, basophils, and dermal Langerhans' cells binds IgE molecules via the CH3 domain.[77-79] Therefore perhaps this part of the IgE molecule has been conserved.

Feline allergic skin disease is thought to be associated with dermal infiltration of Th2 lymphocytes and synthesis of associated cytokines. In a recent study, real-time RT-PCR assays were developed to measure feline interleukin (IL)-2, IL-4, IL-5, IL-6, IL-10, IL-12 (p35 and p40), IL-18, tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), interferon-gamma (INF-γ) and glyceraldehyde-3-phosphate dehydrogenase mRNA in the skin of healthy control cats and in the lesional and nonlesional skin of cats with allergic skin disease.[128] Total RNA was extracted from skin biopsies and cDNA synthesized using Improm-II reverse transcriptase and random hexamers. Real-time PCR was carried out using gene-specific primers designed to span an exon/exon junction of each cytokine gene. Taq-Man probes were used to add specificity to the system. The 11 cytokine mRNA transcripts quantified were present at varying levels, but no apparent difference existed in expression between normal, nonlesional, and lesional skin. TGF-β represented the most abundant transcript, whereas IL-4, IL-5, IL-6, IL-10, IL-12, IL-18, and TNF-α were present at levels approximately 1000-fold less. IL-2 and INF-γ represented the least abundant templates with no detectable copies in most RNA samples. This quantitative analysis of cytokine mRNA expression in feline skin biopsies suggested that no simple Th2 bias exists in lesional skin of cats with allergic dermatopathies.[80,128] This is in contrast to previous studies in the dog, although they used semiquantitative methods for assaying cytokine expression by PCR.[81-83] More recent canine studies in Japan have reported using real-time PCR and detecting cytokines associated with a Th2 response.[84]

In conclusion, atopic dermatitis in cats is still not a well-defined disease; however, initial findings do not contradict a pathogenesis comparable to that described in human beings.

CLINICAL PRESENTATION

The following points should play an important role in the assessment of the clinical signs of cats with suspected AD.

Occurrence

In most cats, signs develop at a young age (6 months to 3 years).[85] In the literature, a wider age range often is reported. However, the age at which cats first developed signs often is not reported, and many studies report on cats that were referred, which possibly influences the data.[12,86,87]

No breed or sex predilections exist for AD, although one author suggested a possible association with Abyssinian cats.[88] A genetic predilection has been described[17,89] and has been observed by the authors.

The disease typically is chronic and characterized by remissions and exacerbations. Signs of disease may be seasonal or perennial. In a referred patient, this history may be influenced by repetitive use of or maintenance therapy with glucocorticoids.

Pruritus

The clinical hallmark of atopic dermatitis in cats is pruritus and more specifically recurrent pruritus that usually is glucocorticoid responsive. Rarely, cats do not respond at all, or only to such high doses of glucocorticoids that they cannot be used for maintenance therapy because of side effects.

Some cats do not exhibit overt pruritic behavior in the presence of the owner; consequently a careful and extensive history is important. In addition, the amount of licking is a subjective assessment, and discerning between normal grooming behavior and overgrooming as a sign of pruritus may be difficult for an owner.

Besides extensive licking, other signs of pruritus may be scratching, biting, nibbling, hair pulling, or rubbing the face with a paw. To discern whether the lesions are self-induced, the body location is important, although cats are supple animals. In rare cases, the history of frequent vomiting of hairs and a trichogram are necessary to confirm a history of pruritus.

Skin Lesions

The type of skin lesion can vary. The clinical manifestation is influenced by the duration of disease, the intensity of pruritus, and the cat's behavior. Nonlesional pruritus may occur initially. Skin lesions described are erythema, papules, and crusted papules (miliary dermatitis), excoriations and linear crusts, exudative lesions, and eosinophilic plaques.

Self-induced alopecia or hypotrichia resulting from broken hairs may be present as sole lesions or often accompany the skin lesions. The coat may be dull or irregular, or may feel damp to the touch.

Eosinophilic plaques may occur as single lesions, or are often found together with other lesions. Eosinophilic ulcers are less common signs of AD unless they occur together with other lesions. The same holds true for eosinophilic granulomas.

Distribution Pattern

When flea-bite hypersensitivity and food adverse reactions have been excluded, many cats with AD exhibit a certain distribution pattern of lesions:

Generally, a symmetrical pattern is found that often includes head, pinnae, and neck, the abdomen extending up to the lateral side of the thorax, flanks, and limbs. Not all cats exhibit skin lesions at all predilection sites at presentation. Skin lesions may be prominent only on the head, but when examined carefully, subtle skin changes often can be found at the other predilection sites as well.

On the head, lesions occur often at the preauricular or periocular areas. The periocular changes may be very subtle and may consist of only erythema and hypotrichia. Erythema and hypotrichia around the lower lips and chin can be confused with signs of acne. In acne, however, the changes are limited to the chin and usually do not extend to the corner of the lips. In addition, pruritus is not a primary sign of acne.

Often the outsides of both pinnae are involved. However, otitis externa with swelling and erythema of the ear canal commonly is not associated with feline AD, unlike the situation in dogs.

Primarily, the proximal part of the limbs is affected, especially the medial-caudal side, which may extend to the caudolateral side. In contrast to dogs, the feet rarely are involved. In contrast to flea-bite hypersensitivity, the lumbosacral area usually is spared.

In some countries, the clinician also should consider the distribution of mosquito-bite hypersensitivity, which includes the paws, nasal area, and dorsal aspect of the head and the pinnae.

Other Signs

The incidence of concurrent, possibly allergic, diseases is unclear. Many studies report on a small number of cats with AD without comparing this population with healthy cats or cats with different diseases.

Sneezing is reported to be an accompanying sign in about 50 per cent of the cases.[7] Although we have seen this sign in cats with AD, whether it occurs more often in connection with AD is unclear. Also, chronic coughing and asthma may occur; however, whether the concurrence of bronchial hyperreactivity is higher in cats with AD compared with other diseases has not been determined.

Concurrence with flea-bite hypersensitivity is often described.[86,87] This finding often is based on partial improvement on a strict flea control program or on a positive intradermal test reaction to flea allergen. The value of the latter test result is debatable, because healthy normal cats exposed to fleas may have a positive test result.[90]

Although concurrence with food adverse reactions is described,[10] our experience and others' testify to its rarity.[91] In cases of concurrent disease, the question may remain whether the other diseases are not well enough controlled, or if the diseases truly concur.

Lymphadenopathy may be found as a sign of chronic skin inflammation. The occurrence of secondary bacterial pyoderma (see Chapter 28) or *Malassezia* infection is uncommon to rare, and usually it does not require antimicrobial treatment.

The presence of blood eosinophilia is a nonspecific finding,[35] and not every cat with AD is eosinophilic[12] (see Chapter 26).

The histopathological reaction pattern of miliary dermatitis, eosinophilic plaques, and pruritic facial and neck dermatoses shares the common changes of dermal infiltration with mast cells, eosinophils, lymphocytes, and macrophages. This archetypal reaction pattern cannot distinguish between flea bite hypersensitivity, food hypersensitivity, and feline AD.[27,28,30,92,93] Furthermore, the various clinical forms of EGC may not be readily distinguished histologically.[37] Flea-bite hypersensitivity reactions also display a wide variety of histological changes; consequently, skin biopsies are not a helpful diagnostic test.[93]

DETECTION OF ANTIGEN-SPECIFIC IgE IN CATS WITH ALLERGIC SKIN DISEASE

Exclusion of food adverse reactions and flea-bite hypersensitivity, when living in a flea-endemic area, always remain part of the clinical workup, before further diagnostic tests are performed, to confirm a diagnosis of AD.

Intradermal testing (IDT) has been the traditional method of demonstrating mast cell–bound reaginic antibodies, presumably of the IgE isotype, that may mediate allergic skin diseases in cats as in other species. The assumption has been that cats may be skin tested with similar allergens and concentrations to those used in dogs, although some cats with no evidence of skin disease may give positive skin reactions, presumably reflecting allergen exposure.[94] Several studies have demonstrated that cats may respond to intradermal tests in a similar manner to dogs.[61,92,94-97] In cats, however, IDT can be frustrating, with a propensity for negative results, in our experience (Table 25-1). Some uncertainty remains about the allergen concentration for intradermal tests. For example, using Greer allergens in cats with *Otodectes* mite infestation, positive intradermal reactions were observed with a 1/5000 w/v dilution of house dust mites *D. farinae* or *D. pteronyssinus.*[100] Austel, et al[97] advocated using less than 1000 PNU/ml concentration for such allergens in cats with suspected allergic disease.[97,100] Codner[96] used a mixture of house dust mite allergens from Greer Labs Inc (Lenoir, NC) and advocated a dilution of 1/1000 w/v as a threshold concentration for cats compared with the 1/10,000 to 1/50,000 w/v threshold used in dogs.

However, Schleifer and Willemse[61] did not find any association between the allergen concentration and the development of response or type of skin test reactivity. Some authors recommend using fluorescein dye to improve visualization of positive intradermal reactions.[61,98,99]

Cats are sedated before testing with ketamine and diazepam,[100] tiletamine-zolazepam,[102] or ketamine and xylazine.[86] We currently use medetomidine (Domitor, Pfizer) followed by atipamezole (Antisedan, Pfizer), both by intramuscular injection. Cats are reported to have weak skin test reactivity. One explanation for this may be that during handling and skin testing procedures, plasma cortisol, corticotropin, and α-melanocyte stimulating hormone concentrations are raised. However, in one study, cortisol was still raised after handling and skin testing procedures despite sedation.[103] Recent drug therapy, inappropriate allergen selection/preparation, and technical difficulties in carrying out the test make intradermal testing of cats a challenge.

The measurement of feline serum IgE is available from a number of commercial laboratories. Although some laboratory systems have been discussed in peer-reviewed journals, few have been validated externally in terms of the specificity and sensitivity of their reagents.[104] One such laboratory uses a polyclonal anti-feline IgE reagent prepared from a chimeric antibody composed of feline heavy epsilon chain and mouse light chain.[105] This test system has been evaluated in a group of feline patients, and the in vitro test results correlated poorly with the final clinical diagnosis, based in part on intradermal testing.[86] A similar study of chronic idiopathic gastrointestinal problems in cats used the same assay, but it was deemed to have limited value as a screening test for suspected food hypersensitivity.[106]

The human FcεRIα protein has been cloned and used extensively for studies of canine IgE[107-111] with limited reports of its use for the detection of feline IgE antibodies.[11,112-114] In these preliminary studies, IgE antibodies were detected to flea allergens in cats without overt skin disease and intermittent flea exposure, and occasionally in normal cats. Substantial differences appeared between dogs and cats in terms of the pattern of reactivity to house dust mite allergens. The FcεRIα protein has a high affinity for binding specifically to IgE molecules; a

Table 25-1 | **Summarizing Results of Intradermal and Serology Testing in Cats at University of Bristol**

ALLERGENS	DP	DF	FLEA	NEGATIVE	POLLEN	TYROPHAGUS
IDT	27	34	29	44	9	Not done
Total number of cats 100	(1)*	(5)	(6)			
ASIS	16 (20%)	32 (40%)	21 (26%)	26 (32%)	26 (32%)	26 (32%)
Total number of cats 82		(16)	(8)			(2)

IDT, Intradermal testing performed according to methods published in references 12,86; *Dp, Dermatophagoides pteronyssinus*; *Df*, *D. farinae*; *ASIS,* Allergen-specific IgE serology (Allercept, Heska).

*Figures in parentheses represent number of cats with positive test with no other allergens implicated.

These data relate to cats skin tested in the UK. Data in other geographical areas may vary as a result of differences in allergen exposure and factors that influence the immune response of cats to such allergens. There were 56 cats tested by IDT and ASIS.

In general, cats with reactions on skin testing to Df also reacted to Dp, and cats that were positive on ASIS to Df also were positive to Dp and Tyrophagus. However, in the UK, Df is considered to be rare, perhaps suggesting that these crude antigens share common epitopes recognized by IgE antibodies, rather than shared antigen exposure.[129]

The dominant allergens seem to be house dust mites, fleas, and to some extent pollen allergens. Even so, 16 of the cats positive on ASIS did not have active skin disease and presumably these results reflect exposure and stimulation of an IgE response to ubiquitous allergens. Also, 26/81 (32 per cent) and 44/100 (44 per cent) were negative with ASIS and IDT testing methods respectively. Of the skin test-negative cats, 20/44 (45 per cent) also were negative by ASIS. These results are somewhat different than those for dogs in the UK, where 16 per cent and 10 per cent of atopic dogs respectively in one study were negative with IDT or ASIS.[110]

theoretical possibility exists for binding of homocytotropic IgG molecules, although this has not been studied in dogs or cats.[109,115]

Recent studies by Taglinger, et al[116] evaluated cats with clinical signs of self-induced alopecia without lesions, miliary dermatitis, eosinophilic granuloma complex, papular/ulcerative dermatitis of head, and neck-facial dermatitis. An ELISA using the FcεRIα biotinylated protein was developed to detect *D. farinae* (DF)-specific and *D. pteronyssinus* (DP)-specific IgE antibodies. No significant difference existed in house dust mite–specific IgE-antibody concentrations between 59 cats with allergic skin disease and the normal control group of 22 cats. The results of the study suggest that it is difficult to relate the concentration of allergen-specific IgE to the different clinical presentations of suspected allergic skin disease in cats. Also, like the studies by Gilbert, et al,[63-65] discordant results may occur in comparison of different methods for the detection of IgE antibodies.

ALLERGEN-SPECIFIC IMMUNOTHERAPY (ASIT)

The diagnosis of feline AD has been considered appropriate in cases of a favorable response to hyposensitization.[4,17,91,117-119] Positive responses to allergy therapy also have been reported based on the results of in vitro testing.[120,121] Certainly, hyposensitization therapy may be valuable in the long-term management of some patients. However, we do not know how this mode of therapy works in cats. A favorable response to desensitization may be due to immune mechanisms that have little to do with IgE-mediated reactions in the skin. Therefore using the response to hyposensitization is not an appropriate method of validating either intradermal or allergen-specific serology data, or a means of establishing a diagnosis of AD in cats. In a review of data from cases seen at the University of Bristol, good responses to ASIT were observed in 7/30, moderate responses in 7/30, and poor responses in 16/30. In six of the latter cases, the initial induction course was not followed up by a maintenance course of ASIT. Overall follow-up periods ranged from 1 to 5 years. A good response implies little if any ancillary therapy; a moderate response implies some resolution of the skin condition with or without ancillary therapy; and a poor response indicates that ASIT was abandoned and regarded as a failure.

The response to ASIT is extremely variable in dogs, and this may reflect the lack of standardization and wide variation in the methods used to assess the clinical response.[122] The criteria used for assessing the clinical outcome for ASIT should be objective, and a validated scoring system needs to be established and applied universally to studies of canine and feline AD.[122,123] Such a scoring system may include several methods to assess the clinical outcome, such as those used to assess the therapeutic response of atopic dogs to cyclosporine A or methylprednisolone.[124] One method used is clinical lesion scores (e.g., the Canine Atopic Dermatitis Extent and Severity Index [CADESI]), and recently some progress has occurred in establishing a validated clinical lesion scoring system for feline allergic skin disease, as reported by Kunkle, et al.[125,126] Given the variable results of reports of ASIT in cats, with small numbers of cases, and with presumed atopic skin disease, a need clearly exists for a multicenter, randomized controlled trial using standardized allergens in terms of both the means of diagnosis (intradermal or allergen-specific serology) and immunotherapy protocol.

CONCLUSION

The problem with considering the term feline atopic dermatitis as a clinical diagnosis is that a number of confounding factors make the use of the term debatable. These factors include data sets gathered primarily on small groups of cats, with no clear indication for an inherited basis. In laboratory studies, the control cats may include laboratory cats that may not be exposed to house dust mites as are household cats. The clinical presentation varies considerably, and the chronicity of lesions may have influenced the results of studies. The role of IgE in disease pathogenesis remains obscure, notwithstanding concerns expressed about the specificity and sensitivity of reagents used to detect such IgE. In addition, the estimated efficacy of immunotherapy is based on open studies, which are difficult to assess especially because the disease can wax and wane.

Although the name atopic dermatitis is now well established in veterinary dermatology, it may not be justified when considering feline patients. Debate continues regarding the nomenclature for human allergic diseases.[127] Perhaps one compromise would be feline allergic dermatitis syndrome (FADS), within which is a subgroup in which allergen-specific IgE can be detected. Clearly much remains to be learned about our feline cases with presumed allergic skin disease.

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Chapter 26

EOSINOPHILS AND EOSINOPHILIC DISEASES

Karen M. Young and Karen A. Moriello

Eosinophilic dermatitis is the generic term used to describe any skin disease in which eosinophils are the predominant cell type. Eosinophilic dermatoses occur in many species but are common particularly in cats. For years these diseases were considered to be definitive diagnoses, but they now are recognized to be reaction patterns that can result from any number of etiological triggers. Despite the frequency with which these skin diseases occur, only now are we beginning to understand the role of the eosinophil in the development of these diseases. The goal of this chapter is twofold: (1) to review clinically important information and highlight new information about eosinophils, particularly feline eosinophils, and (2) to briefly review the clinical presentations of feline eosinophilic diseases and highlight clinically relevant new information about this "old" set of feline skin diseases.

THE EOSINOPHIL

The eosinophil is a bone marrow–derived leukocyte that takes its name from an affinity for anionic dyes, such as eosin.[1] Because eosinophils can dampen and enhance inflammatory reactions, they can serve beneficial and detrimental roles. For example, they play a role in defense against helminthic parasites and in diminishing inflammation mediated by basophils and mast cells; however, because of the toxicity of their granule constituents, they can mediate significant damage to host tissues. Determining which of these roles eosinophils are serving in any given disease presents many challenges, including how to approach therapeutic intervention. An understanding of the eosinophil's structure-function relationships provides a basis for making this determination. Several comprehensive reviews provide more detailed information.[2-8]

Production and Distribution of Eosinophils

Bone marrow is the main site of eosinophil production, although development also occurs in the thymus, spleen, and lymph nodes in some laboratory species.[9] A distinct progenitor cell, the colony-forming unit-eosinophil (CFU-EO), gives rise to developing eosinophils in response to coordinated expression of multiple T cell–derived cytokines, including interleukin (IL)-3, granulocyte/macrophage colony-stimulating factor (GM-CSF), and IL-5.[10,11] IL-5 is the most eosinophil-specific cytokine and promotes the differentiation, proliferation, maturation, survival, and function of eosinophils.[12-13] Initial characterization of feline IL-5 suggests homology with the human cytokine.[14] In bone marrow, the first recognizable eosinophil precursor is the eosinophilic progranulocyte containing specific, or secondary, eosinophilic granules. Granules continue to accumulate in myelocytes, and both granule and nuclear maturation continues in metamyelocytes, bands, and segmented eosinophils. Eosinophils make up less than 10 per cent of the nucleated cell population in bone marrow and differentiate and mature in 2 to 6 days, depending on the species; this time may be shortened in animals with heightened eosinophilopoiesis. Their half-life in circulation varies from less than 1 hour in the dog to up to 18 hours in human beings, and migration into tissues occurs randomly.[15,16] Eosinophils reside in tissues, especially in the loose connective tissue of organs such as skin, respiratory tract, and gastrointestinal tract, which serve as portals for foreign substances and antigens. Their lifespan in tissue is approximately 6 days in people, but this time can lengthen under the influence of cytokines, such as IL-5, which inhibit apoptosis and therefore prolong eosinophil survival.[2,4,8,13]

Morphology

Light Microscopic Appearance

The mature eosinophil is slightly larger than a neutrophil and has a bilobed or trilobed nucleus and, in cats, numerous rod-shaped granules. The granules house potent cytotoxic proteins, and because of the intensely basic nature of these proteins, the granules stain red-orange with the acidic dyes found in Romanowsky stains, such as Wright's or Wright-Giemsa stains (Figure 26-1, *A*). Quick Romanowsky stains, such as Diff-Quik, may impart a similar tinctoral quality to the granules but sometimes the granules fail to stain or stain poorly with quick stains, and eosinophils may be mistaken for neutrophils. Basophils, which in cats contain gray or lavender granules, often are found in the company of eosinophils (Figure 26-2). Mast cells,

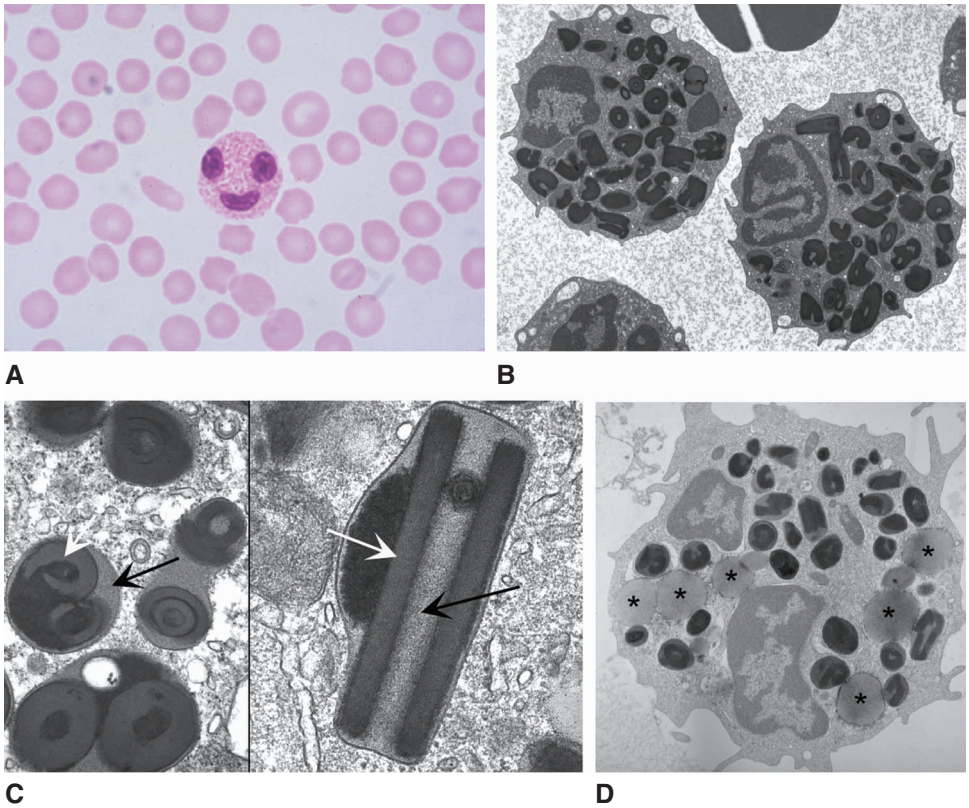

Figure 26-1. Feline eosinophils. **A,** Eosinophil in peripheral blood. Granules are rod-shaped and stain orange-red with Romanowsky stains. Wright's stain, ×100 objective. (Photomicrograph courtesy of Dr. Charles K. Henrikson.) **B,** Two eosinophils containing numerous heterogeneous bicompartmental granules. Transmission electron micrograph, original magnification ×4500. **C,** Bicompartmental secondary eosinophil granules in cross section *(left)* and longitudinal section *(right)*. *White arrows* indicate the core or crystalloid, and *black arrows* indicate the matrix. Transmission electron micrograph, original magnification ×40,000. **D,** Activated eosinophil from a cat with allergic bronchitis. Asterisks (*) indicate lipid bodies. Transmission electron micrograph, original magnification ×9100. (Transmission electron micrographs by Dr. Richard L. Meadows.)

neutrophils, macrophages, lymphocytes, and plasma cells also can be found in tissues with eosinophilic inflammation.

Ultrastructure

Eosinophils contain multiple organelles, including mitochondria, free ribosomes, sparse RER, coated vesicles, a small Golgi, glycogen particles, and lipid bodies, which are spherical stores of arachidonic acid used to generate leukotrienes and prostaglandins.[17,18] However, the granules are the most prominent feature and comprise four separate types: specific granules, primary granules, small dense granules, and microgranules. Of these, the specific, or secondary, granules are the most numerous (see Figure 26-1, *B*). In cats, and in human beings, rhesus monkeys, goats, rabbits, opossum, guinea pigs, rats, and mice,[2,15,17] the specific granules have two compartments, termed the core and the matrix. The core is electron-dense, has longitudinal and cross-sectional periodicity, and in cats is widely variable in terms of density, size, shape, and location within the granule. A more lucent matrix typically surrounds the core but may fall in the center of the granule (see Figure 26-1, *C*).

Constituents of Specific Granules

A group of highly cytotoxic proteins are found within the granules and have been characterized fully in guinea pigs and human beings.[18,19] The four principal proteins are *major basic protein* (MBP), *eosinophil peroxidase* (EPO), *eosinophil cationic protein* (ECP), and *eosinophil-derived neurotoxin* (EDN). MBP is located in the core of the granule, represents more than half of the granule protein content, and is a potent cytotoxic protein with activity against helminths, bacteria, protozoa, and mammalian cells. Deposits of MBP can be found at

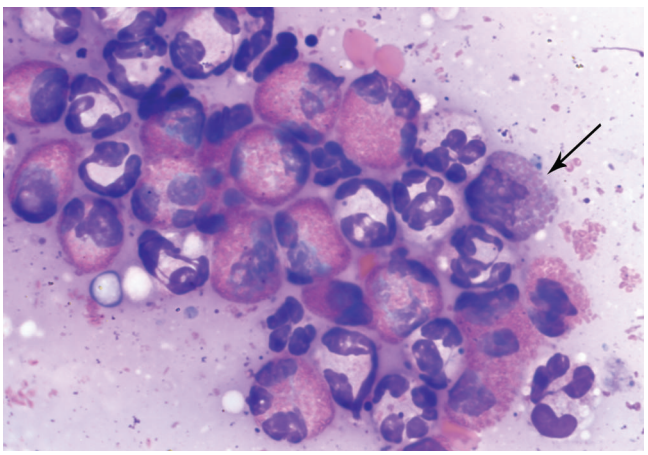

Figure 26-2. Imprint of skin from a cat with exudative pruritic skin disease. Cells are a mixture of eosinophils and neutrophils. The *arrow* indicates a basophil. Wright's stain, ×100 objective.

sites of eosinophilic inflammation. The matrix of the granule contains the other three proteins. EPO is distinct from and more potent than myeloperoxidase and has activity against helminths, bacteria, and mammalian cells.[7] ECP constitutes slightly less than a third of the protein found in granules; has activity against helminths, bacteria, and mammalian cells; is a neurotoxin; and has RNase activity. It damages membranes by a colloidal osmotic process and causes formation of transmembrane non–ion-selective pores. EDN has greater RNase activity than ECP and damages myelinated nerve fibers but has little or no cytotoxic action on parasites or mammalian cells. In addition to these four major proteins, granules contain other constituents, including oxidation enzymes and metallic ions.[18] In cats, EPO has been reported absent in eosinophil granules based on cytochemical studies.[20,21] However, in a recent study of the biological activities of proteins from feline eosinophil granules, peroxidase activity was demonstrated in one of the three protein peaks eluted from the granules.[22] In addition, a single MBP and RNase activity (associated with ECP and EDN) were identified, and similarities with human granule proteins were observed.

Other Granules

Primary granules are numerous at the progranulocyte stage but decrease in number as the eosinophil matures. These granules contain lysophospholipase activity, which diminishes inflammation by inhibiting the formation of arachidonic acid metabolites. This activity is located in the Charcot-Leyden crystal protein (CLCP), a protein that may be found in polymerized form as hexagonal crystals deposited in tissues at sites of eosinophilic inflammation, even when intact eosinophils are no longer visible.[23] The small dense granules in eosinophils contain acid phosphatase, arylsulfatase, and perhaps ECP, catalase, and peroxidase. Lastly, microgranules, also termed vesiculotubular structures (VTS), are unique eosinophil organelles and are membrane-bound structures that transport cytotoxic proteins from their site of synthesis within the cell to specific granules, thereby protecting the cell from the toxic effects of these potent proteins. VTS also may play a role in degranulation by delivering proteins from the granule to the tissue or target, which leaves an empty granule behind.[18]

Structure-Function Relationships in Eosinophilic Inflammation

Eosinophils, containing numerous preformed toxins, leave circulation, enter tissues, and migrate to their destination, guided by interactions between their surface molecules and mediators, such as adhesive molecules and chemotactic factors, in the tissues. Along the way, eosinophils are primed, or "preactivated," a process that enables the cell to react to stimuli with little or no effect on the naive cell. Important primers, derived from both B and T lymphocytes, include the cytokines IL-3, GM-CSF, IL-5, and IL-4, which mediates ε isotype switching and rapid production of IgE.[24] Priming and subsequent activation lead to adhesion, chemotaxis, deregulation, release of lipid mediators, and oxidative burst. Chemoattractants include C5a, N-formyl-methionyl peptides, leukotrienes, platelet-activating factor (PAF), hydroxyeicosatetraenoic acids (HETEs), hydroxyheptadecatrienoic acids (HHTs), MCP-3, MIP-1α, ECF-A, histamine, parasite-derived factors, and chemokines such as RANTES.[4-5,25] Many of these factors also recruit neutrophils, monocytes, and other inflammatory cells; eotaxin, a chemokine acting synergistically with IL-5, is more selective for eosinophils.[26,27] IL-5 also promotes eosinophil survival by preventing apoptosis in addition to repriming/reactivating listless eosinophils to a proinflammatory state.[5,6,13] Because many types of inflammatory cells follow these same pathways, mixed inflammation is common. However, in some disorders, such as parasitic infection and hypersensitivity disorders, eosinophils predominate because of several eosinophil-selective processes, including adhesion (mediated by VLA-4/VCAM-1), priming (mediated by IL-5), chemoattraction (mediated by eotaxin), and prolongation of survival (mediated by IL-5). A major consequence of chronic eosinophilic inflammation is tissue damage, which may be reversible or permanent once fibrosis ensues.[3,5,28,29]

Effector Functions

Eosinophils serve a number of effector functions depending on the milieu in which the cells locate. Both preformed and newly synthesized mediators are released as the eosinophil fulfills its function. The role of eosinophils in defense against helminthic parasites remains controversial. Certainly, basic toxins and hydrolytic enzymes are released directly onto the target parasites, and oxidative bursts contribute to antihelminthic actions; however, in mice in which eosinophils and IL-5 were ablated, parasite burden and resistance to infection did not worsen, which calls into question the effectiveness of the eosinophil response.[30,31]

Modulation of inflammation is a second effector function. During hypersensitivity reactions, eosinophils remove immune complexes and granular debris released from mast cells, inactivate mediators released by basophils and mast cells and inhibit their degranulation, and prevent the generation of active metabolites.[5] However, this modulatory effect may be most important under homeostatic conditions and may be more limited in mast cell–mediated inflammation.[2,32]

In asthma and allergic disease, eosinophils cause tissue damage in late phases of these disorders by releasing proinflammatory mediators, such as leukotriene C4, PAF, and eicosanoids, and granule proteins. For example, MBP is toxic to airway epithelium and mediates bronchial hyperreactivity. Recruitment is associated with allergen-induced release by CD4+ lymphocytes of IL-5 and GM-CSF, cytokines that also enhance effector function and prolong survival of eosinophils, which prevents the termination of eosinophilic inflammation.[33-35] IgE-mediated mast cell degranulation, induced upon reexposure to allergens and parasite antigens, also plays a role in eosinophil recruitment in hypersensitivity disorders.[4] Eosinophils also are capable of phagocytosis, and immune complexes, antibody-coated erythrocytes, mast cell granules, inert particles, yeast, and bacteria, including *Mycoplasma* organisms, have been found in eosinophils, although neutrophils are clearly much more efficient at killing bacteria. Another function of eosinophils is tumor cytotoxicity; however, the mechanisms are unclear. In some neoplasms, local infiltration by eosinophils in the absence of peripheral eosinophilia improves prognosis.[36,37] Finally, eosinophils may participate in T cell–mediated immunity and may contribute to wound healing or sclerosis and fibrinolysis.[16,38-40]

Eosinophils accomplish their effector functions through degranulation, occurring via piecemeal degranulation, exocytosis, or cell necrosis,[18] release of lipid mediators, such as PAF, leukotrienes (LTB4, LTC4), thromboxane A2, prostaglandins (e.g., PGD2, PGE, PGF1, and PGF2α),[4,5,41] and cytokine release. Lipid mediators may contribute to host dysfunction, such as bronchial hyperreactivity.[5,42]

Activated eosinophils can be recognized by morphological changes, cell surface characteristics, and functional activities.[4,18,28] These changes typically are found in tissue eosinophils, although in human patients with allergic disease and hypereosinophilic syndrome, activated eosinophils may be found in circulation. Morphological changes include a decrease in the number of granules leading to hypodensity[43] and increased numbers of lipid bodies and VTS. Lipid bodies serve as a repository of arachidonate-containing lipids for oxidative metabolism and synthesis of lipid mediators, and VTS are increased to deliver granule products to the tissues, which results in a decrease in the specific granule content. Activated feline eosinophils have similar changes (see Figure 26-1, *D*). Other changes noted in human eosinophils are increases in primary granules that contain CLCP; small, dense granules; and other vesicles and tubules. Functionally, cytotoxicity to parasites and mammalian cells is increased; generation of reactive oxygen species is enhanced, and enzymes such as acid phosphatase are activated.

Eosinophilia

The concentration of eosinophils in peripheral blood can be determined in several ways. The least accurate is multiplication of the total leukocyte count by the percentage of eosinophils based on a manual differential leukocyte count performed on a stained blood film. However, this method is useful in most situations. Eosinophil counting chambers also can be used. Automated methods that stain peroxidase provide the most accurate counts in most species; however, eosinophil peroxidase is not detected by this method in cats. The reference interval for eosinophils varies among species and geographical regions.

Eosinophilia results from elaboration of eosinophilopoietic factors, principally IL-5, by T cells sensitized by parasite antigens or allergenic antigens elaborated in atopy, drug allergy, and asthma. Chronic eosinophilia is associated with inflammatory disorders of mast cell–rich organs, namely skin, lungs, gastrointestinal tract, and uterus (see Figure 26-2). Importantly, eosinophilia is not always present in the face of eosinophilic inflammation in tissues in which eosinophil survival is increased. Some neoplasms, such as lymphoma, mast cell tumor, and solid tumors, are associated with eosinophilia caused by tumor cell elaboration of IL-5 and other cytokines.[44] Eosinophilic leukemia is a rare disease, and the diagnosis depends upon ruling out other causes and measuring serum IgE levels. In hypereosinophilic syndrome (HES), characterized by persistent idiopathic eosinophilia, increased survival of eosinophils in circulation, tissue infiltrates, and organ dysfunction, a proposed mechanism of eosinophilia is clonal expansion of T cells generating eosinophilopoietic factors.[29] Increased levels of IL-5 in these patients may override the apoptotic effects of corticosteroids, which results in steroid resistance. In recent studies of human beings with chronic eosinophilia, a fusion tyrosine kinase has been identified in some patients, leading to a proposed algorithm for diagnostic testing and treatment.[45] Patients positive for the fusion gene are classified as having clonal eosinophilia, for example, chronic eosinophilic leukemia. Those negative for the gene are considered to have chronic eosinophilic leukemia, HES, or T cell–associated HES, and these diseases must be distinguished by additional laboratory testing or therapeutic trials.

Novel therapeutic approaches to eosinophilic inflammation are being investigated and include anti–IL-5 antibody, receptor antagonists, inhibitors of eosinophil chemotaxis and IgE synthesis, and corticosteroids that act more specifically to affect adhesion and production of proinflammatory cytokines.

CLINICAL UPDATE ON SELECT DISEASES

Clinical Presentation

The following is a brief update on recent findings about these "old" diseases.

Miliary Dermatitis

Miliary dermatitis refers to a papulocrusting dermatitis that presents clinically as small erythematous crusting papules. This skin disease has long been recognized in cats and now is recognized as a cutaneous reaction pattern rather than a diagnosis. Until recently, parasitic and allergic etiologies have been considered the primary causes. However, these lesions increasingly are being recognized as clinical signs of feline bacterial or yeast pyoderma[46] (Figure 26-3).

Indolent Ulcer

Indolent ulcer is a unilateral or bilateral erosive lesion on the upper lip of cats of any age. Recently emerging evidence shows a possible genetic predisposition in some cats to develop lesions when exposed to allergic triggers, particularly fleas.[47,48] Another interesting finding is that these lesions also can occur as a result of foreign bodies (cactus spines) or at the site of a focal insult, that is, on the lip margins at the sites where dermatophyte-infected hairs, stick-tight fleas, or ticks previously have been found.[49,50] Indolent ulcers as a result of focal traumas are transient and often one-time occurrences; this may explain

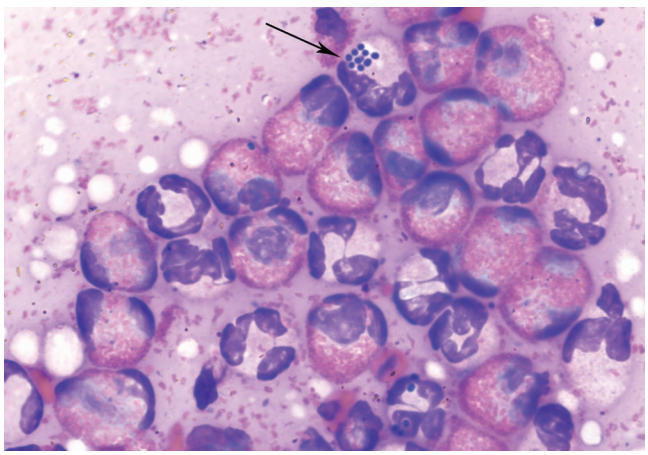

Figure 26-3. Imprint of skin from a cat with exudative pruritic skin disease (same cat depicted in Figure 26-2). The *arrow* indicates numerous bacterial cocci in a neutrophil. Wright's stain, ×100 objective.

why in some cats, particularly young kittens, lesions may develop and resolve without treatment and not recur. Lesions that persist or are recurrent are caused by a persistent trigger such as atopy or food allergies.

Eosinophilic Plaque

Eosinophilic plaques are intensely pruritic, erosive, exudative, raised lesions of varying size. Close inspection of many eosinophilic plaques often reveals that cats have concurrent "miliary dermatitis–like lesions" or that the plaques are a coalescence of these papulocrusted lesions. The most important recent finding is that these lesions increasingly are being recognized as the feline equivalent of canine pyotraumatic lesions (i.e., "hot spots"), and secondary bacterial and/or *Malassezia* spp. overcolonization is a common cytological finding.[46,50] Lesions are the direct result of self-trauma and commonly are seen on the face, abdomen, inguinal region, medial and caudal thigh areas, and neck. These lesions are triggered most commonly by an itch-scratch event, and recurrent lesions are often, but not always, the hallmark of an underlying allergic disease. These lesions also can develop as a result of infections: dermatophytosis, bacterial infections, and *Malassezia* infections.

Eosinophilic Granuloma

Eosinophilic granulomas are the only "true granuloma variant" of feline eosinophilic diseases. Two recognized clinical variations exist. The first is an ulcerated, proliferative lesion often present in the oral cavity. Depending upon the location of the mass, dysphagia, drooling, abnormal mastication, and coughing may be present. The other form is characterized by a hard, noninflammatory swelling. Alopecia is variable and the cat seems unperturbed by the lesion. Clinical presentations include linear pencil thick lesions on the caudal thigh of young cats, linear lesions on limbs, "fat lips" or asymptomatic chin swelling, 1- to 5-mm firm, papular lesions on the ears of cats, and interdigital masses.

Mosquito-Bite Hypersensitivity/Insect-Bite Hypersensitivity

Mosquito-bite hypersensitivity/insect-bite hypersensitivity is characterized by a papular erosive eruption on the face, ear tips, nose, and footpads of cats (see Chapter 25). Lesions tend to start in the thinly haired areas and may be more common in dark-coated cats. The lesions are intensely pruritic and depigmentation, crusting, and exudates may occur. The lesions were first noted in cats exposed to mosquitoes, but can result from the bites of other small flying insects such as black flies and *Culicoides* spp. Typically the cat has access to the outdoors especially during the early morning or evening hours when these insects are feeding. Many of these biting insects are small enough to get through the holes used to screen most outdoor porches and windows. Although symmetrical ulcerative facial lesions are the most commonly described clinical signs in individual case reports, a study of 26 cats from Japan found that the most commonly observed lesions were miliary dermatitis such as lesions on the ear pinnae.[51] "Crusties" on the ear margins are common client complaints, and this report suggests that prevalence of insect-bite hypersensitivity may be underrecognized.

Familial Eosinophilic Lesions

Familial eosinophilic lesions have been described in specific pathogen–free laboratory cats by at least two investigators.[47,48] These cats developed lesions between 4 and 18 months of age and they were observed to recur until the cats were at least 4 years of age. In one study, 21 out of 24 cats descended from these cats developed lesions.[47] The lesions tended to be most common during the spring and summer, which suggests a possible seasonal allergen trigger, insect trigger, or hormonal or reproductive trigger. A hereditary predisposition to eosinophilic lesions is not unexpected, particularly those with allergic etiologies. Canine atopy has long been recognized to be heritable and feline atopy recently has been described in three littermates.[52]

Diagnosis

Eosinophilic skin lesions in cats are, almost without exception, reaction patterns. The real challenge is not the clinical recognition of the reaction pattern, but rather of the underlying trigger. It is not within the scope of this chapter to discuss the diagnosis of these underlying causes and the reader is referred to general dermatology references for information on this topic.[53,54] Chapter 30 provides an update on current information on histological findings.

Symptomatic Treatment Options

Antimicrobial Therapy

Glucocorticoids have long been touted as the initial treatment of choice for these lesions, especially for any of the "exudative" eosinophilic dermatoses. In the past, antibiotic therapy was recommended for cases that did not respond to systemic glucocorticoids. These "antimicrobial responders" were considered a rarity, and response to treatment was attributed to the antiinflammatory effects of the antibiotics. Glucocorticoids long ago were abandoned as a first-line therapy in the treatment of dogs with pruritic exudative lesions. We now are recognizing that this also may be the initial best treatment of choice for cats. Prior reluctance to using antimicrobial therapy as a first-line treatment was based upon the fact that impression smears from these lesions primarily were eosinophilic and not neutrophilic as they are in dogs. Impression smears of these lesions may reveal predominantly eosinophilic inflammation with intracellular and/or extracellular bacteria or yeast. This is in contrast to what is seen in cases of canine pyoderma, in which neutrophilic exudate is a hallmark of pyoderma or yeast dermatitis.

In addition, in both species, the role of bacterial and/or yeast colonization or overgrowth still remains somewhat unclear. Are these organisms the cause or the result of the self-trauma and inflammation? This dilemma may be academic because it is clearly obvious to clinicians that even if these organisms do not cause the disease, they play a significant role in perpetuation of the lesions. Secondary infections should be resolved before glucocorticoid therapy is instituted.

YEAST INFECTION

Itraconazole therapy (5 to 10 mg/kg PO q24h) for 15 to 30 days

Terbinafine can be used but at 40 mg/kg PO q24h

BACTERIAL INFECTION

Trimethoprim sulfa (30 mg/kg PO q12h)
Cephalexin 20 mg/kg PO q8-12h
Doxycycline 10 mg/kg PO q24h for 21 to 30 days

Antihistamines

Antihistamines most commonly are used as adjunct therapies to control pruritus. They are used alone and/or in combination with glucocorticoids. They probably are most helpful for the humane relief of pruritus in cats that receive antimicrobial therapy.

Cetirizine is an antihistamine shown to have significant effects on eosinophil migration in human beings. In a double-blind study in human beings, it was shown to decrease wheal formation and pruritus significantly.[55] This drug may be useful in the management of eosinophilic diseases either alone or with glucocorticoids. Because it may interfere with eosinophil migration, it is not recommended for use in cats before a skin biopsy procedure. The oral dose is 5 mg/cat PO q12-24h. Fenoxofenadine 2 mg/kg PO q12-24h is another antihistamine that may be useful as adjunct antipruritic therapy.

Cyclosporine A

Cyclosporine is an oral immunosuppressive drug used to prevent rejection of organ transplants. Anecdotal reports testify to its usefulness in the treatment of eosinophilic plaques, indolent ulcers, and oral granulomas.[56] The most common adverse effect is vomiting or diarrhea. Dividing the daily dose and administering the drug with food can minimize this complication. The drug comes in two formulations. The modified cyclosporine formulation must be prescribed because it is better absorbed. Two common initial drug doses are 2.5 mg/kg PO q12h, or 25 mg/cat q24h or divided q12h. Evidence of improvement usually is seen within 10 days of initiation of therapy.

The drug is recommended as an alternative to glucocorticoid therapy in cats and should not be used concurrently with ketoconazole, itraconazole, fluconazole, erythromycin, or methylprednisolone, because this may increase toxicity. In obese cats, the ideal rather than the actual body weight should be used for calculation of total drug dosage because obesity in human beings is associated with increased toxicity. Plasma or serum concentrations are not monitored when used at this low dose; the key aspect of monitoring is response to therapy.

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Chapter 27

DEMODICOSIS

Daniel O. Morris and Karin M. Beale

Compared with canine demodicosis, little is known about the feline disease. It commonly is considered a relatively "rare" parasitism, although awareness of the disease is increasing. Demodicosis may present with a wide variety of clinical signs and therefore is an important differential diagnosis for nearly every inflammatory reaction pattern known to affect feline skin. The two species of mites responsible for the disease are known to occupy separate ecological niches in the skin; a factor that appears (at least in part) to determine the dominant clinical signs.

DEMODEX CATI

Clinical Signs and Differential Diagnosis

Demodex cati is a long, slender mite similar in morphology to *Demodex canis* (the most common causative agent of canine demodicosis) (Figure 27-1). The habitat of *D. cati* is the hair follicle and sebaceous glands/ducts. Like its canine counterpart, *D. cati* provokes follicular inflammation, and in doing so may result in any combination of alopecia, follicular plugging (comedones), scale, crusts, and even erosion/ulceration[1] (Figures 27-2 and 27-3). Large numbers of mites tend to be found at the site of clinical disease, which suggests that lesions develop as a result of an exploding mite population. The distribution of skin lesions is variable but involves the head/face and distal limbs most commonly. Generalized disease appears to occur less commonly than with canine demodicosis. The mite also may inhabit the external ear canals and cause a ceruminous otitis externa, which is variably pruritic. Some cases exhibit pruritus comparable to ear mite infestation, whereas others are mild. Otitis may present as the sole clinical manifestation of the disease or in conjunction with more widespread skin lesions. Therefore, important differential diagnoses for *D. cati* infestation include dermatophytosis, pemphigus foliaceus, bacterial folliculitis, *Notoedres cati* (feline sarcoptic mange), *Otodectes cynotis* (ear mites), and some of the more unusual causes of erosive and ulcerative dermatitis (such as drug eruptions, squamous cell carcinoma, and epitheliotrophic T-cell lymphoma). In addition, pruritus associated with *D. cati* is relatively common, and it may be confused with a primary allergic disease, especially when concurrent otitis externa is present.

Pathophysiology

The pathophysiology of *D. cati* infestation is unknown. The mite is part of the naturally occurring microfauna of feline skin, and mite reproduction to the point of causing dermatitis may be associated with an underlying systemic disease (retroviral infection, diabetes mellitus, neoplasia) or iatrogenic immunosuppression (glucocorticoids, cancer chemotherapy).[1,2] Localized immunosuppression (resulting from squamous cell carcinoma *in situ*) also has been implicated as a predisposing cause.[3] However, some patients with *D. cati* infestations have no apparent underlying disease or predisposing drug use. Although our understanding of the canine immune response to *D. canis* is relatively advanced, studies evaluating the cell-mediated and humoral immune responses of cats to *D. cati* have not been performed.

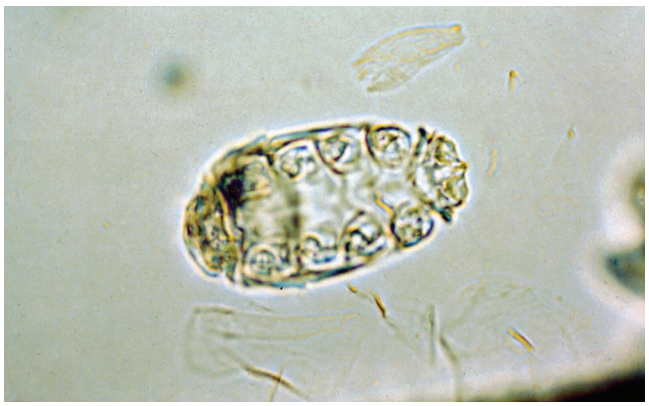
DEMODEX GATOI

Clinical Signs and Differential Diagnosis

Demodex gatoi is a short, broad species that inhabits the stratum corneum (the most superficial layer) of the epidermis (see Figure 27-1). The primary clinical sign resulting from parasitism by this species is pruritus, and the intensity of the pruritus is suggestive of a hypersensitivity response. Resulting skin lesions are typical of the cutaneous reaction patterns associated most commonly with feline allergic dermatoses: self-inflicted symmetrical alopecia, miliary dermatitis, and the eosinophilic dermatitis complex (i.e., eosinophilic plaques, indolent lip ulcers, and eosinophilic granulomas) (Figures 27-4 and 27-5). Symmetrical alopecia is by far the most common presentation of infested cats.

Occult cases of *D. gatoi*, which are often the most pruritic, appear to be common. This is similar to the clinical progression of canine scabies and is further evidence of a hypersensitivity component. The scarcity of mites on many pruritic cats with *D. gatoi* easily can lead to a missed diagnosis (see below). Most pruritic cats likely are removing the mites physically (by licking), which makes the mites difficult or impossible to find with routine skin scrapings. The difficulty in finding these mites on skin scraping, and the ease with which they can be overlooked, are other important factors that can contribute to misdiagnoses.

A



B

Figure 27-1. A, *Demodex cati.* **B,** *Demodex gatoi.*

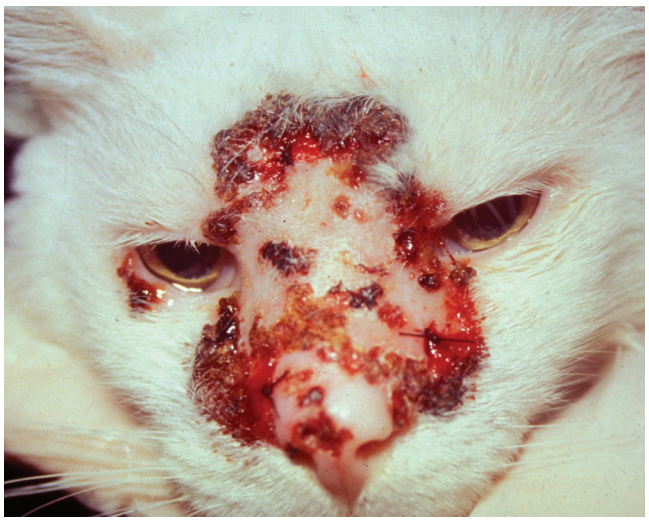


Figure 27-2. Severe ulcerative facial dermatitis due to *D. cati* in an 8-year-old domestic shorthair cat with renal lymphosarcoma, anemia, and thrombocytopenia. Biopsies were performed to rule out *Cryptococcus neoformans* and the demodex mites were discovered instead.

An additional and very important feature of this parasite is the fact that some infested cats demonstrate no clinical signs whatsoever, which further supports the possibility that the pruritus induced in affected cats may be associated with a hypersensitivity response to the parasite. Because not all affected cats in a household show clinical signs, the feline housemates of

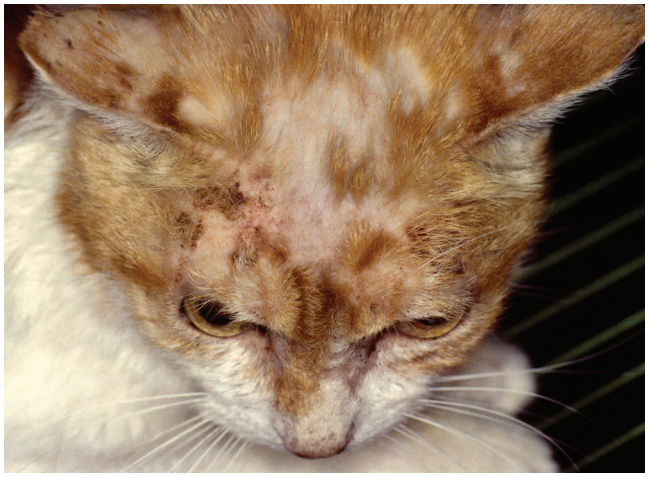


Figure 27-3. Patchy alopecia with miliary dermatitis and crusting resulting from *D. cati* in a 6-year-old domestic shorthair cat. No predisposing cause was identified.

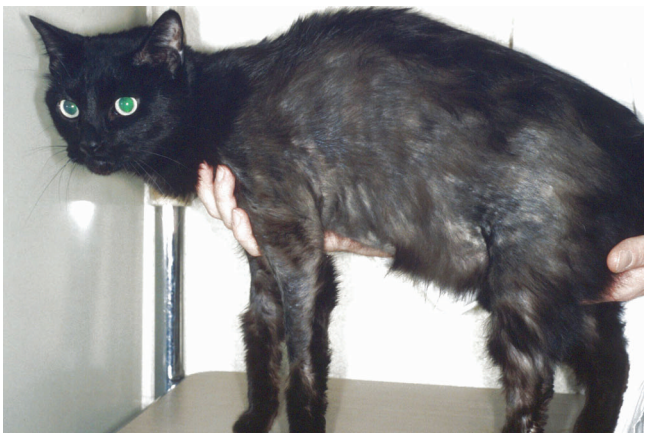


Figure 27-4. Self-inflicted symmetrical alopecia resulting from *D. gatoi* infestation of a 3-year-old domestic shorthair cat. The cat had received injectable methylprednisolone acetate before diagnosis. After clearing the mites, hair regrowth was complete but facial pruritus persisted. A diagnosis of adverse food reaction eventually was made.

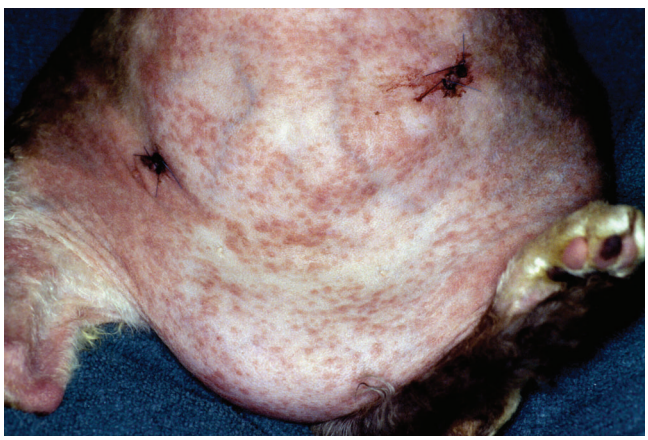


Figure 27-5. Self-inflicted alopecia with papular eruption of the abdomen, resulting from *D. gatoi* in a 10-year-old cat. Note suture sites: biopsies were performed to rule out cutaneous T-cell lymphoma.

affected cats always should be screened for parasitism (see below). The distribution pattern of *D. gatoi* infestation is variable, but the ventral abdominal and flank regions are affected most commonly. However, facial and acral lesions (similar in distribution to *D. cati*) also may occur, as can otitis externa.[1] Any cat with suspected "psychogenic alopecia" or idiopathic pruritus should be screened for *D. gatoi*. The differential diagnosis must also include atopic dermatitis, adverse food reaction, flea bite allergy dermatitis, cheyletiellosis, *Otodectes cynotis* and, in the case of miliary or plaque lesions, dermatophytosis and cutaneous neoplasia.

Transmission

A unique feature of *D. gatoi* infestation is an apparent risk for contagion among cats via casual contact. Given the highly contagious nature of the disease and its spread among cats in a shelter facility that allowed limited contact between cats, limited fomite transmission could occur.[4] Most infested cats have a history of going outdoors or may have been adopted from a shelter. This is the only demodex species of domestic mammals for which horizontal transmission through casual contact has been reported.[5]

Pathogenesis

Like *D. cati*, the pathophysiology of *D. gatoi* infestation is largely unknown. Most cases reported in the literature have had histories of glucocorticoid therapy, although whether this is truly a risk factor for the development of disease is unclear.[1] Although *D. gatoi* commonly has been diagnosed as a "secondary" problem in isolated indoor cats that were receiving some form of glucocorticoid therapy (often as treatment for a primary allergic disease), it also has been the primary diagnosis for cats with no history of glucocorticoid treatment, but with histories suggestive of contagion (such as roaming cats or those obtained from shelters). Other sources of systemic or localized immunosuppression have been reported in conjunction with *D. gatoi* infestation, including retroviral infection, diabetes mellitus, and cancer chemotherapy. The authors also have documented cases in association with localized cutaneous neoplasia or dysplasia, including epitheliotrophic T-cell lymphoma and actinic keratosis.[1] In these cases, mites were identified on top of the plaque lesions. Therefore any pruritic cat with cutaneous neoplasia should be screened carefully for both *Demodex* spp.

Whether *D. gatoi* is part of the normal microfauna of feline skin is unknown, although definitive diagnosis suggests an extremely marked regional variability in its occurrence on cats within North America. Over a 7-year period in our practices, only two cases of *D. gatoi* have been presented to the dermatology service at the University of Pennsylvania (northeast United States),* whereas at a referral dermatology practice in Houston, Texas (south-central United States),† several cases are diagnosed each month.

*Personal observation of one of the authors of this chapter, Daniel O. Morris.
†Personal observation of one of the authors of this chapter, Karin M. Beale.

Diagnosis (Both Species)

The diagnosis of *D. cati* usually is straightforward because numerous mites typically are found. Because it lives in hair follicles, deep/concentrated scrapings (to the point of causing capillary ooze) are necessary. The skin should be squeezed gently to express mites toward the surface between cycles of scraping, until a generous amount of blood and debris is collected. For areas more difficult to scrape (such as eyelids, toes, and interdigital spaces) hair plucks sometimes are successful, because mites may be dislodged along with the hairs. In heavily crusted or ulcerated areas, skin biopsy may reveal the diagnosis and help rule out other differential diagnoses (see Figure 27-2). In rare cases, low numbers of mites can make diagnosis more difficult. Although *D. cati* is part of the normal cutaneous microfauna, even a single mite should be considered suspicious when collected from a compatible skin lesion. If no other explanation for the lesion is found, treatment should be instituted on a trial basis.

In cases involving *D. gatoi*, in which occult infestation is common, a single mite found from the composite of multiple scrapings is diagnostic. A scraping technique similar to that used for scabies is appropriate: broad, superficial scrapings of large surface areas. In endemic areas or suspect cases, negative scrapings should not be trusted. Alternative measures include fecal flotation (pruritic cats appear to groom away and ingest the mites) and therapeutic trials (see below). We also have found mites adhered to the cellophane tape used to collect skin impression cytology samples.

Again, all in-contact cats should be screened for infestation. Even if negative skin scrapings are obtained from healthy in-contact cats, treatment of all in-contact asymptomatic (i.e., "unaffected") cats still is recommended because of the possibility of occult infestation. If an owner is reluctant to treat all cats, the infested patient should be isolated during the treatment period. The owner should be aware, however, that reinfestation is possible when treatment is stopped, if the other cats happen to be harboring an occult infestation.

Regardless of the mite species involved, cats with demodicosis should be screened for retroviral diseases by serology and for other systemic diseases if indicated by attendant clinical signs. For pruritic cats that have received glucocorticoid therapy previously, a final diagnosis must be reserved until miticidal treatment is finished because some may have another primary pruritic dermatosis.

Treatment

The recommended treatment for infested cats is a series of six weekly lime sulfur dips (LymDyp, DVM Pharmaceuticals, Miami, FL). A concentration of 2 per cent is effective, but failures with 1 per cent solutions have been documented.[1] Unfortunately, this product is not available in the United Kingdom. The haircoat should be saturated and cats should "soak" in the lime sulfur for a minimum of 5 minutes. The topical solution should not be rinsed off, and the cats should be allowed to air dry. An Elizabethan collar is recommended to prevent ingestion of the dip while drying. Lime sulfur causes a temporary discoloration of light-colored fur and is terribly malodorous while wet.

Cats typically demonstrate significant clinical improvement after three treatments; however, mites still may be present on

skin scrapings at this time. After the third dip, some cats may experience an increase in scaling and pruritus, which most likely is due to the drying (or potentially irritating) effects of the dip itself. This usually resolves rapidly after the sixth and final dip.

Cats with negative findings on skin scrapings that have symmetrical alopecia and are on appropriate flea control may have an occult infestation with *D. gatoi.* A therapeutic trial with three lime sulfur dips is recommended. If the cat shows improvement after the third dip, a full series of six dips is recommended, and other household cats should be dipped as well. If the cat is not better by the third week, it is unlikely that the pruritus is due to demodicosis.

Because of the aesthetically unappealing nature of lime sulfur dips, many owners are reluctant to use this treatment, and other options have been used. Treatment with once-weekly ivermectin has been ineffective for both species of mites. Once daily, or every-other-day ivermectin at 300 µg/kg PO is effective in treating both species of mites. For *D. cati*, treatment should be continued until negative scrapings are obtained. For *D. gatoi* infestation, the authors recommend treatment for 2 weeks past resolution of clinical signs with a minimum of 6 weeks of treatment. Because of the potential for toxicity with ivermectin (including Heinz body anemia resulting from the propylene glycol vehicle), lime sulfur is preferred over daily or every-other-day ivermectin treatment.

We have treated two cases with daily milbemycin oxime (Interceptor, Novartis Animal Health, Greensboro, NC) at a dose of 1 mg/kg PO daily, without effect. Selamectin (Revolution, Pfizer Animal Health, Exton, PA) has been evaluated systematically in the treatment of *D. gatoi*. Unfortunately, selamectin was ineffective on a weekly basis in the treatment of this mite.[6]

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Chapter 28

BACTERIAL PYODERMA

Anita Patel

Pyoderma is a pyogenic bacterial infection of the skin, which, despite its name, is not always characterized by the presence of pus or pustules. The bacteria involved in the infection may form part of the cutaneous microflora or may be transient or opportunistic species introduced during grooming, or through contamination of a wound inflicted while fighting or hunting. Little information has been published on feline pyoderma, whereas canine pyoderma has been well documented. Canine pyodermas have been classified as superficial or deep, depending on the depth of the infection and further subclassified according to the lesion type, anatomical site, and/or distribution.[1] Unfortunately, because of the paucity of reports on cats and because they are prone to exhibiting reaction patterns rather than specific lesions, or specific regional distribution, application of the same classification to cats is impossible.

Classification of feline pyodermas into two groups would be more appropriate, based on depth and type of lesions present. They can be divided into *superficial* pyodermas, in which the predominant lesion type are crusted papules, plaques, scaling, excoriations, and ulcerations; and *deep* pyodermas, in which the lesions include abscesses, nonhealing draining nodules, ulcers, and cellulitis. Depending on the etiological agent, an overlap between the superficial and deep bacterial infections may be observed.

Feline pyoderma may be classified further as *primary* or *secondary*, depending on whether an underlying or associated disease is identified. Primary infections are uncommon to rare, they respond to treatment, and they do not recur. Secondary infections usually are associated with immunological diseases, hypersensitivities, and hormonal disorders. Previously, pyoderma has been associated with immunosuppressive conditions such as feline immunodeficiency virus and feline leukemia virus infections. Hypersensitivity and immune dysregulation, resulting from diseases such as diabetes mellitus, neoplasia, and hyperthyroidism, also may be responsible for secondary skin infections. The role of staphylococci, in particular, as secondary pathogens has been well documented in canine pyoderma[2] but not in the feline disease. The role of staphylococci as secondary pathogens is discussed later in this chapter.

The host skin immune system and the epidermal structure normally provide an epidermal barrier; however, the thin nature of the stratum corneum and its reduced lipid content have been implicated as one reason for the high incidence of staphylococcal infections in dogs.[3] Similarly detailed knowledge of skin structure unfortunately is not available in cats.

Few reports implicate the role of bacteria in perpetuation of feline skin disease, and pyoderma generally has been considered uncommon to rare. However, anecdotal reports frequently mention dermatoses in cats that respond to antibiotic therapy. Bearing in mind the differences in the lesion types and the grooming responses of cats to pruritus, pyoderma possibly goes largely unrecognized, especially as a secondary infection.

This chapter discusses the role of cutaneous bacteria in pyoderma, its pathogenesis, and its clinical presentations, in addition to the diagnosis and treatment of bacterial infections, based on the depth of infection and type of inflammatory reactions present.

SUPERFICIAL PYODERMA

In this chapter, this term is used to describe infections confined to the epidermis and the follicular epithelium. It encompasses clinical presentations with the predominant lesion types of crusted papules, plaques, scaling, excoriations, and ulcerations and the conditions commonly known as acne, superficial juvenile pustular dermatitis, superficial pyoderma, and superficial folliculitis.

Cutaneous Bacteriology

Knowledge of the cutaneous bacteriology of feline skin is useful in understanding the pathogenesis of pyoderma. However, until recently, little information has been available on cutaneous bacteriology in diseased, or even in healthy, feline skin. The skin and hair form a microbial barrier and provide a microclimate ideal for the survival of resident microorganisms. Resident bacteria are those organisms that live in symbiosis with each other, without any detriment to the host. Transient microorganisms are those that, once seeded onto the surface through grooming or contact, do not normally multiply, unless the host defenses are debilitated locally or systemically. A microorganism may be resident at one site (e.g., the nares) and transient at another (e.g., the hair coat).

For many years, *Staphylococcus aureus* and *Staphylococcus simulans* were reported as the most prevalent coagulase-

positive and coagulase-negative species, respectively, isolated from cats.[4,5] In a semiquantitative study conducted by Cox et al,[6] *Staphylococcus intermedius* was found to be the coagulase-positive species isolated most frequently from the coats of healthy cats; however, because *S. intermedius* was categorized previously as a biotype of *S. aureus,* these findings may not be in conflict. In the same study, *S simulans* was the coagulase-negative species isolated most often.

S. simulans, found frequently on human skin, has been reported as having a resident status on cats.[5,6] Igimi et al[7] suggested that, in the past, many of these isolates might have been the coagulase-negative species, *Staphylococcus felis,* which was first described in 1989. The two species have similar biochemical properties, but they are distinguished by differences in mannose fermentation, phosphatase reaction, and bacitracin sensitivity.[8]

A recent study[9] reported on the prevalence of cutaneous staphylococci in three groups of cats: feral cats, healthy pet cats, and pet cats with skin lesions. This study found no significant difference in the isolation rates of staphylococci between the feral cats and the normal or affected pet cats, but a significant difference between the normal pet cats and the affected pet cats. This study distinguished between *S. simulans* and *S. felis* by comparing profiles of the isolates in the study to those of the type strains of *S. felis*[7] using a commercial API ID32 Staph. test (API Biomerieux). *S. felis* was isolated from skin and mucosal sites in all three groups of cats, and no significant difference existed between the groups, which suggests that the organism has a resident status in cats. *S. felis* also has been isolated from saliva, skin, and conjunctivae of cats.[10-12] Other resident organisms isolated in the earlier studies included *Micrococcus* species, α-hemolytic *Streptococcus* species, and *Acinetobacter* species.[4]

S. intermedius was the coagulase-positive species isolated most often from clinically normal cats[6] and from cats with skin lesions.[9] Earlier studies,[4,5] in which *S. aureus* was the most isolated coagulase-positive species, did not biotype the species; therefore the possibility remains that these organisms were *S. intermedius,* which had been considered to be biotypes E and F of *S. aureus.* The residency status of this organism in cats remains unclear (compared with dogs), but it could be considered transient.

Pathogenesis

Superficial bacterial infections involve mainly the organisms that are either part of the cutaneous and/or mucosal microbiota or are introduced into a lesion from the environment or from carrier sites (e.g., by grooming). Nasal carriage is an important factor in introducing staphylococci onto skin sites in human beings and dogs.[13,14] In one report in cats,[15] the same *S. felis* strain was isolated from the nostrils as from the skin lesions, which suggests that the organism was transferred onto these lesions during grooming.

The factors that influence the complex cutaneous microclimates and macroclimates in turn will influence the cutaneous microflora. These factors include environmental conditions, such as temperature and humidity; host factors, such as skin structure, coat type, anatomical site, skin pH, skin secretions, and underlying diseases; and microbial factors. The role of these factors is well documented in dogs, but little is known in cats. Immune competence appears to be an important determinant in the pathogenesis of feline skin infections, but the exact mechanism is not known.

Gram-positive infections caused by staphylococci are the most common cause of cutaneous infections in human beings and dogs, mainly causing superficial infections. A small study[16] in cats on the potential role of staphylococci in the pathogenesis of pruritic skin lesions showed that five of the nine cats in the study responded to antibacterial therapy alone and management of the underlying condition. The response to antimicrobial treatment, in this study, suggests that secondary staphylococcal infections occur in cats.

Interaction between host and microbial factors leads to colonization. The staphylococci must adhere to the epidermal cells for colonization to occur. Staphylococcal adherence to epidermal cells from atopic dogs is significantly greater than those from normal dogs[17]; however, no such information exists on cats.

Staphylococci are capable of producing toxins, enzymes, and other factors that aid colonization and thus disease.[18] Coagulase, an enzyme, has been associated with pathogenicity, because it clumps the bacteria and interferes with their phagocytosis by leukocytes. The pathogenic staphylococcal species *S. aureus*, *S. intermedius*, and *S. hyicus*, which affect mainly human beings, dogs, and pigs, respectively, are coagulase-positive. Until recently, *S. aureus,* a coagulase-producing species, has been implicated in feline lesions; however, more recent studies show that *S. intermedius* is more likely to be involved. Exotoxins and hemolysins from coagulase-negative organisms have been recognized increasingly as associated with human lesions, especially in immunoincompetent patients. *S. felis*, a coagulase-negative species, has been implicated in the pathogenesis of otitis externa,[19] paronychia,[20] and papulocrustous lesions[16] in cats. Although the virulence factors produced by *S. felis* are not known, they may play a secondary role in the pathogenesis of superficial pyoderma.

The potential role of staphylococci in perpetuating skin lesions resulting from excessive grooming as a result of allergic, parasitic, and systemic disease should be considered in all cases. Secondary staphylococcal infections have been associated with paraneoplastic syndromes such as exfoliative dermatitis associated with thymoma, pancreatic alopecia, and metabolic epidermal necrosis associated with pancreatic carcinomas. Their pathogenesis is not understood fully but is likely to be associated with immunodysregulation.

Pasteurella multocida, a common inhabitant of the oral cavity and respiratory tract, can infect skin transiently.[21] It can cause subcutaneous abscesses and superficial purulent skin infections.

Dermatophilosis is a rare condition in cats.[22] It is caused by *Dermatophilus congolensis* and is characterized by formation of crusts and exudative pustular dermatitis. Dermatophilosis is mainly a large animal disease, particularly in tropical countries. Temperature, humidity, moisture, and maceration of the epidermis are important factors in the pathogenesis of the disease. Furthermore, trauma and bites from insects and ticks contribute to the spread of the infection. The crusts are a source of infection.

In my experience, superficial bacterial skin infection in cats follows injudicious use of corticosteroids and progestagens such as megestrol acetate and medroxyprogesterone. Common belief acknowledges these drugs do not have the same side effects in cats as in dogs and that cats tolerate them well.

However, in some cases, repeated use results in immunosuppression, leading to secondary bacterial skin infections. Recently, in an unpublished study,[23] administration of long-acting glucocorticoids has been associated with congestive cardiac failure. Anecdotal reports suggest that bacteriuria and lower urinary tract disease result in self-induced ventral abdominal alopecia, which is responsive to antibacterial therapy.

Clinical Signs

In my opinion superficial pyoderma is an underrecognized skin disease in cats, partly because it presents as reaction patterns and does not have the same classic clinical presentations commonly seen in dogs. The clinical signs of superficial pyoderma vary and include crusted papules, plaques, scaling, alopecia, excoriation, and/or ulcerations (Figures 28-1 through 28-4). The lesions may be present individually or in combination. Pruritus and self-induced alopecia occur in most cases. Although pustules and epidermal collarettes may be seen in some cases, they are rare and tend to be associated with cats that have received corticosteroid treatments. Hyperpigmentation, comedones, and follicular papules may be seen in some patients. Generalized scaling, crusting, and ear disease may be seen in more chronic cases and in particular when associated with a systemic disease. In some cases, self-induced alopecia may be the only presenting sign.

In the past, these lesions have been encompassed in a reaction pattern description such as miliary dermatitis, eosinophilic granuloma complex, and head and neck excoriations. These patterns are common in cats, and they occur mainly with hypersensitivities and parasitic conditions. However, bacterial involvement has been implicated as a secondary cause because, in some patients, the lesions have resolved completely or improved markedly with antibacterial treatment.

Miliary dermatitis refers to crusted or excoriated papules on the trunk, mainly on the dorsum, with varying degrees of self-induced alopecia and pruritus.

Eosinophilic granuloma complex includes eosinophilic plaques, eosinophilic ulcers, and eosinophilic granulomas (see Chapter 26). Eosinophilic plaques, which may be individual,

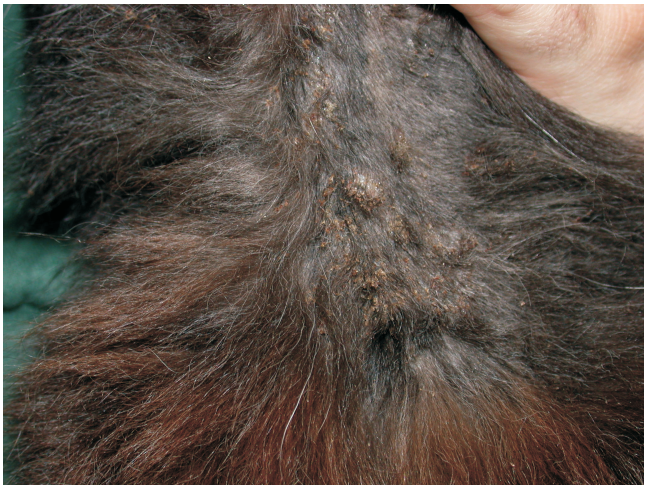


Figure 28-1. Crusted papules on the ventral neck with staphylococcal pyoderma.

Figure 28-3. Scaling that responded to antibacterial treatment. (Photo courtesy Karen Moriello.)

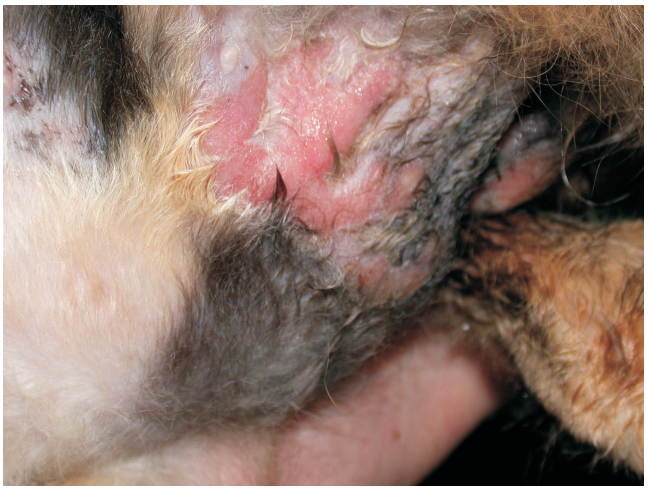


Figure 28-2. Raised eosinophilic plaque with secondary staphylococcal infection in a cat with flea bite allergic dermatitis.

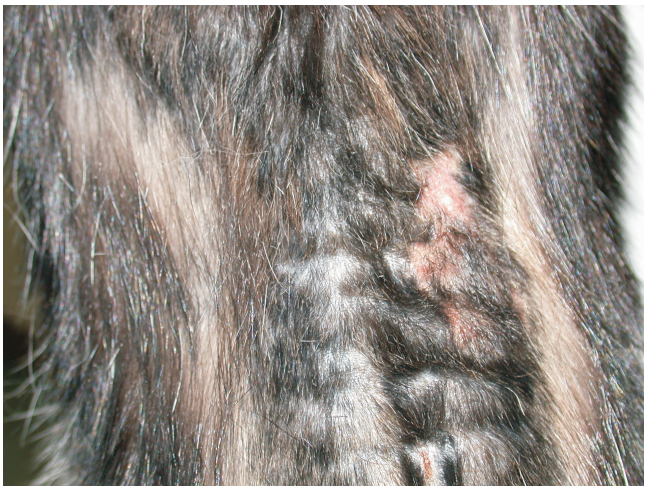


Figure 28-4. Excoriations, alopecia, and lichenification in a cat with staphylococcal colonization. Primary disease was flea bite allergic dermatitis.

Table 28-1 | **Differential Diagnosis of Superficial and Deep Pyoderma in Cats**

DEPTH OF PYODERMA	LESION TYPES	DIFFERENTIAL DIAGNOSIS AND/OR UNDERLYING DISEASE
Superficial	Papules, crusted papules, plaques, crusting, excoriations, comedones, hyperpigmentation, scaling, alopecia, ulceration, epidermal collarettes	*Parasitic:* cheyletiellosis, *Otodectes* infestation, pediculosis, notoedric mange, sarcoptic mange, demodicosis *Infectious*: dermatophytosis, *Herpesvirus* infection, poxvirus infection, leishmaniasis *Hypersensitivity:* flea bite allergic dermatitis, atopic dermatitis, food intolerance, mosquito bite hypersensitivity, tick bite hypersensitivity *Autoimmune:* Pemphigus foliaceus, bullous pemphigoid *Immune-mediated:* cutaneous and systemic lupus erythematosus, erythema multiforme, exfoliative dermatitis associated with thymoma *Sterile idiopathic ulcerative dermatitis*
Deep pyoderma	Nonhealing abscesses, cellulitis, nodules, draining fistulae, ulceration	*Bacterial:* atypical mycobacterial and mycobacterial infections; nocardiosis; actinobacillosis; *Arcanobacterium pyogenes* (previously known as *Actinomyces pyogenes*) infection; *Rhodococcus equi* infection; staphylococcal, streptococcal or *Pseudomonas* pyogranuloma *Fungal subcutaneous mycoses:* phaeohyphomycosis, pythiosis, dermatophyte or eumycotic mycetoma; systemic mycoses (sporotrichosis; cryptococcosis, histoplasmosis, blastomycosis, coccidioidomycosis) *Viral:* poxvirus infection, herpesvirus infection *Neoplastic:* fibrosarcoma, squamous cell carcinoma, lymphoma, mast cell tumors *Sterile idiopathic nodular panniculitis*

several, ulcerated, and/or coalesced, usually are seen on the abdomen and medial thighs. Eosinophilic (rodent) ulcers usually are observed as varying degrees of ulceration on mucocutaneous junctions, especially the lips. Eosinophilic granulomas may occur on the caudal thighs, oral cavity, and the hard palate. The lesions are circumscribed, raised, and have a yellowish to pink surface. They can occur in a linear chordlike pattern on the caudal thigh, also referred to as linear granuloma. Frequently, cats are presented with varying degrees of self-induced alopecia, papules, excoriations, and ulcerations involving the head and/or neck.

Acne is seen commonly in cats of all ages and is thought to be a primary keratinization defect with secondary bacterial involvement. However, some cases may be associated with hypersensitivity disorders, demodicosis, and dermatophytosis. Early signs include comedone formation and a black exudate on the chin and the lower lips. Erythema, swelling, papules, pustules, and furunculosis may develop as the disease progresses.

Paronychia, an infection of the claw bed, has been associated with staphylococcal infections secondary to immunosuppression, trauma, autoimmune diseases, and foreign bodies. Signs include erythema, swelling, and purulent or brown waxy discharge around the nail and the nail bed. The nails may be deformed, broken, or brittle.

In addition to these dermatological signs, peripheral lymphadenopathy and systemic signs associated with specific conditions such as viral diseases, diabetes mellitus, internal neoplasia, and hyperthyroidism may be present on general physical examination.

Differential Diagnosis

Primary superficial bacterial infections, other than cat-fight abscesses, are uncommon and in most cases are secondary to a concurrent disease. Therefore the list of differential diagnoses is extensive and includes all diseases associated with the cutaneous reaction patterns seen in cats (Table 28-1).

Diagnosis

Unlike in dogs, a diagnosis of superficial pyoderma in a cat cannot be based merely on history, clinical signs, and the distribution of lesions. Cytological examination of smears, cultures, histopathology, and response to treatment should be used to diagnose and assess the role of bacterial infections in any case.

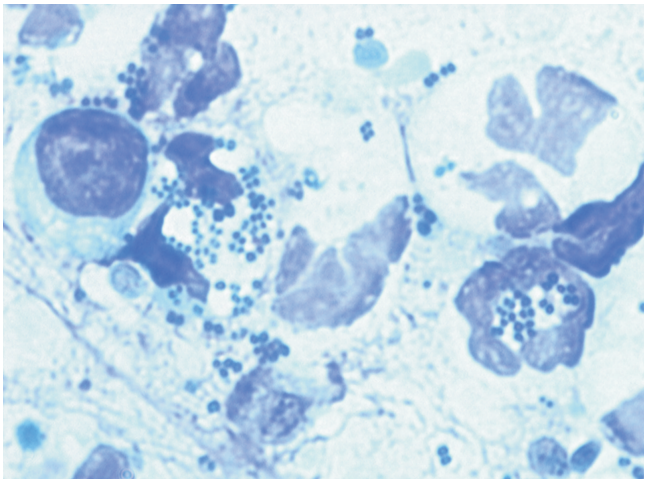
Cytology

Direct impression smears, or tape-strip preparations, taken from the lesions provide valuable information in the investigation of possible superficial infections. Smears are stained with modified Wright's stain (Diff-Quik) and the preparations examined under the oil immersion lens of the microscope. The findings usually provide clues on the pathogenic process involved. The smears may show neutrophils and intracellular cocci or rods suggesting a bacterial infection (Figure 28-5, *A* and *B*). The presence of eosinophils and neutrophils with cocci suggests an infection with a concurrent allergic disease (Figure 28-5, *C*). The presence of bacteria, especially coccal organisms, without phagocytosing neutrophils could be surface contamination but does not rule out microbial overgrowth, and therefore a therapeutic trial is indicated to assess the role of the organisms in the pathogenesis of the lesions.

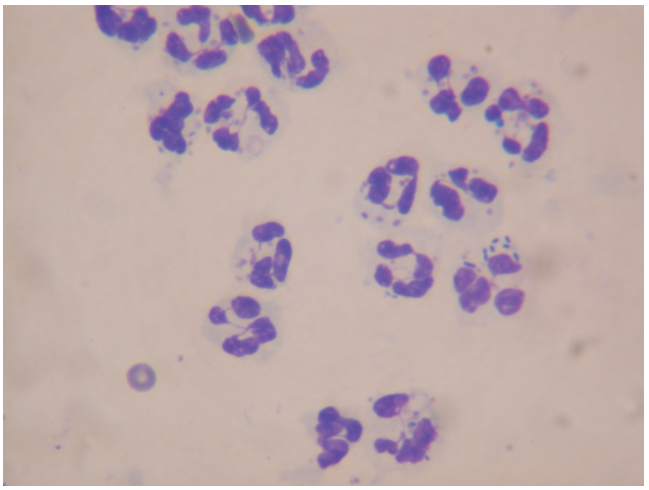
Culture

This is an underused aid in diagnosing the cause of feline lesions, possibly because little information existed until recently regarding the secondary role of bacteria in perpetuating feline lesions.

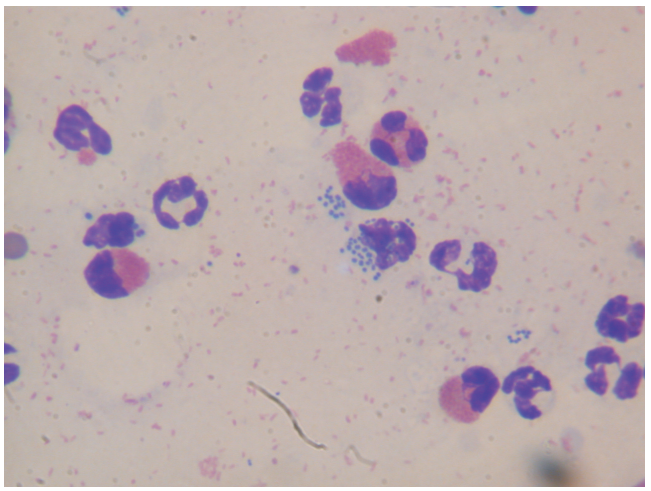
For many years, coagulase-positive staphylococci isolated from feline lesions were assumed to be *S. aureus*. In more recent studies, *S. intermedius*, previously classified as biotypes E and F of *S. aureus*, has been isolated predominantly from



A



B



C

Figure 28-5. A, Impression smear from excoriation showing neutrophilic inflammation with intraneutrophilic cocci. **B,** Impression smear from a pustular lesion on the skin showing neutrophilic inflammation with intraneutrophilic rods. **C,** Impression smear from a plaque showing mainly eosinophilic inflammation with the presence of intraneutrophilic cocci. Note free eosinophilic granules from degranulated eosinophils.

lesions, which suggests these are the most likely pathogenic staphylococci in cats.

Because of commercial pressures, typing the organism is not always viable when a sample is submitted, and species identification is not always performed. In these cases, laboratories may simply report a finding of coagulase-negative staphylococci and suggest that the organism is not pathogenic. However, trial treatment is recommended in cases of cytological evidence of active infection.

Skin Biopsies

Histological findings of skin biopsies may vary, depending on the type of lesions. The findings range from mild to severe neutrophilic and/or eosinophilic superficial perivascular and/or ulcerative dermatitis, interstitial dermatitis, periadnexal dermatitis, perifolliculitis, and luminal folliculitis. Bacteria may be visible in the focal or multifocal crusts on the ulcerated surface or in the stratum corneum (Figure 28-6, *A*). In my experience, the latter is a more common histological finding than presence of pustules or follicular pathology (Figure 28-6, *B*). Histological changes associated with eosinophilic dermatitis and paraneoplastic syndromes may be evident, which gives an indication of the associated primary disease.

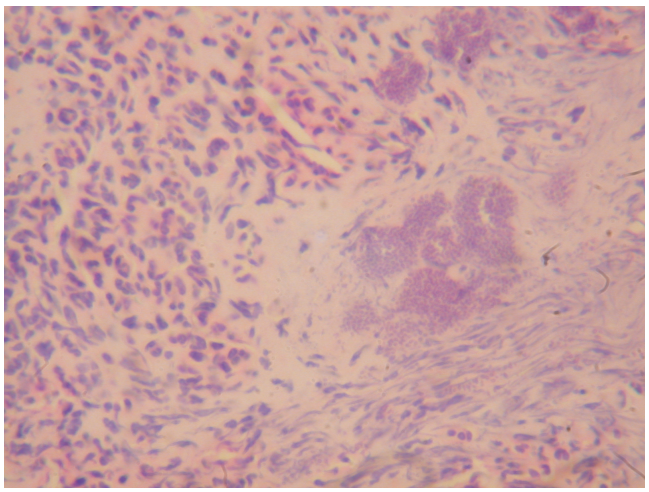
Treatment

Ultimately the significance of staphylococci, or other organisms, depends on the response to appropriate antibacterial treatment. Because the bacterial infection is likely to be a perpetuating factor in skin lesions, rather than a cause, the associated primary disease also must be identified and treated concurrently, if the recurrence of lesions is to be avoided.

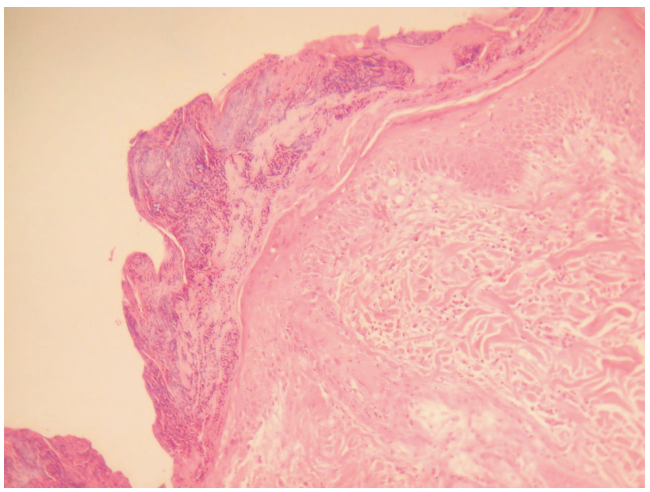
Systemic treatment is best for superficial bacterial infections, given the propensity of cats to lick off most topical medications and the difficulty in bathing them. Several factors should be considered before deciding on the actual antibiotic preparation to prescribe. Unlike dogs, few cats will eat food with medication in it and some drugs may cause the cat to froth and salivate, after which administration of the preparation is impossible. Therefore the ability and the willingness of the owner to administer the medication may be the key to the choice of drug. In affected cats therefore, the therapy must be individualized to suit owner and patient.

A few reports[11,24,25] exist regarding the antibacterial susceptibilities of the staphylococci found on cats, and the drugs and dosages recommended for the treatment of superficial pyoderma based on these reports can be found in Table 28-2. Staphylococcal resistance to penicillin and amoxicillin appears to be common in the United States and the United Kingdom. Therefore these should be not used as a first line of treatment. However, because of regional differences, they may be useful in other geographical locations. Treatment always should be carried out for 7 to14 days beyond clinical cure.

Underlying diseases should be investigated and treated. In most cases it is best to monitor progress much more frequently in cats than in dogs, because concurrent antiinflammatory treatment is required in some cases. In particular, concurrent treatment is required for the resolution of the lesions in cases with eosinophilic dermatitis.



A



B

Figure 28-6. A, Coccal bacterial colonies within the crusts as seen on histological section stained with H & E stain. **B,** Subcorneal pustule in a cat with bacterial infection in a cat with exfoliative dermatitis associated with a thymoma.

DEEP PYODERMA

This term describes conditions in which the infection has invaded the dermis and the subcutaneous tissue, via either a ruptured follicle or a penetrating wound. The lesion types seen in cats include abscesses, furuncles, nonhealing draining nodules, ulcers, and cellulitis.

Pathogenesis

The bacteria may be introduced into the dermis, or subcutis, through broken skin, or may extend from the epidermis and the follicle. Infections extending from the surface normally involve organisms that form part of the cutaneous microenvironment and are associated mainly with staphylococci; however, other organisms also may become involved during the progression of the disease. Organisms introduced into the skin through penetrating wounds, commonly resulting from a fight,[26,27] usually are from the oral cavity. They include aerobic bacteria *Pasteurella multocida*, staphylococcus species, *E. coli,* and β-hemolytic streptococci; and anaerobic organisms such as *Bacteroides*, *Actinomyces* spp. (now known as *Arcanobacterium* spp.), and *Clostridium* spp. In most cases, the infections lead to abscess formation and in some cases cellulitis.

Saprophytic bacteria may be introduced through wound contamination. *Nocardia* spp.,[28] *Rhodococcus equi,*[29,30] and saprophytic mycobacteria may be involved.[31-33] The latter has been covered extensively in volume 4 of this series.

Saprophytic organisms have a tendency to cause deep infections leading to pyogranulomatous to granulomatous dermatitis in both immunocompetent and immunosuppressed cats. The organisms develop several strategies to survive within the host tissue. They may do so by inhibition of the bactericidal effects of lysosome or by preventing fusion between it and the phagosome, or by multiplying intracellularly, thus circumventing the host defense mechanisms. Also, they may possess cell wall components that are resistant to the effects of lysosomal enzymes. In such situations, the production of interferon gamma (IFN-γ) by activated T cells in an effort to remove the

Table 28-2 | **Systemic Agents for Superficial and Deep Bacterial Infections in Cats**

ANTIBIOTIC	DOSAGE*	ROUTE OF ADMINISTRATION
Amoxicillin-clavulanic acid†	12.5-25 mg/kg q12h	PO, IM, SC
Cephalexin†	15-20 mg/kg q12h	PO
Cefadroxil†	20 mg/kg q12h	PO
Clindamycin†	5.5 mg/kg q12h	PO
Doxycycline‡	5-10 mg/kg q24h	PO
Enrofloxacin‡	5 mg/kg q24h	PO, SC
Marbofloxacin‡	2-5 mg/kg q24h	PO
Lincomycin†	20 mg/kg q12h	PO
Penicillin G§	10000 IU/kg q12h	IM
Oxytetracycline†	10-30 mg/kg q12h	PO
Trimethoprim-sulfadiazine†	15-30 mg/kg q12h	PO
Clofazimine‡	2-8 mg/kg q24h	PO
Rifampicin‡	10-20 mg/kg q12h	PO

PO, oral; *IM,* intramuscular; *SC,* subcutaneous.
*q12h, every 12 hours; q24h, every 24 hours.
†Useful for superficial pyoderma
‡Useful for deep pyoderma based on the identification of the causative organism and sensitivity to the agent.
§Used for actinobacillosis, *Arcanobacterium pyogenes* infection, and nocardiosis. Some of the agents are not approved for veterinary use.

organisms leads to the activation and accumulation of macrophages and neutrophils within the tissue, which in turn leads to the formation of granulomas and/or pyogranulomas.

Clinical Signs

The clinical signs include abscesses, cellulitis, draining furuncles and sinuses, nodules, and nonhealing ulcers. Abscesses and cellulitis are common and usually are a result of cat fights. They may occur anywhere on the body but are seen mainly on the face, neck, and tail base. They appear as a soft, fluctuant swelling, which usually is painful, and on close examination bite wounds or scabs may be found under tufts of matted hair. In some cases, these swellings rupture and a purulent discharge is seen. Cellulitis is seen mainly in the distal limbs as a diffuse painful swelling and, depending on the duration of the disease, the skin may be red to blackish in appearance and devoid of hair. Systemic signs include pyrexia, inappetence, and malaise.

Bacterial furunculosis is an uncommon presentation in cats and presents as papules, pustules, ulcerations, and draining fistulas with varying degrees of pain and pruritus. The lesions may occur anywhere but are seen most frequently on the chin region and sometimes have been described as acne.

Nonhealing lesions, nodules, ulcers, and draining tracts are seen mainly in cases associated with saprophytic bacteria, which have gained entry through wounds that have become contaminated with soil or other debris (Figure 28-7). The causative agent cannot be identified by the clinical presentation alone. Lesions develop slowly over a period of weeks to months and often are unresponsive to routine treatment used for abscesses and superficial infections. They range from single circumscribed nodules to multiple ill-defined swellings with draining fistulae and punctate ulcers. Lesions may occur anywhere on the body, but the most common sites are the abdominal, thoracic, and lumbosacral regions. The discharge varies from purulent to hemopurulent and may contain granules.

The condition may be pruritic and/or painful. Peripheral lymphadenopathy may be a feature in some cases. Systemic illness may be associated with the infection in some cases, especially with certain etiological organisms. Systemic signs, such as dyspnea associated with pyothorax, anorexia, weight loss, weakness, pyrexia, and lethargy, may be present, depending on where the infection may have disseminated to internal organs. Hypercalcemia is associated with granulomatous infections in cats[34] (see Chapter 17).

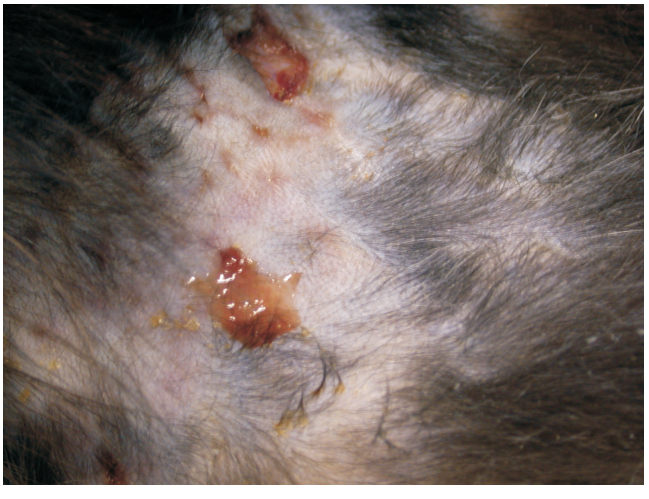


Figure 28-7. Draining sinuses, crusting, ulcers, and alopecia on the lateral trunk caused by concurrent *Mycobacterium fortuitum* and *Nocardia asteroides* infection.

Differential Diagnosis

Depending on the lesion types present, the differential diagnosis includes viral, fungal, neoplastic, and immune-mediated conditions (see Table 28-1). In many cases, differentiation between the diseases based on history and clinical signs alone is impossible without performance of diagnostic tests.

Diagnosis

Both pathogenic and saprophytic bacteria can become involved in the pathogenesis of deep pyoderma, ulcers, nodules, nonhealing abscesses, and cellulitis. The diagnosis is based on the history, clinical signs, and laboratory investigations. Identification of the organism involved by culture is the standard in such cases. These infections are uncommon and can occur in cases of systemic disease; therefore hematological, biochemical, and serological tests for immunosuppressive diseases, such as feline immunodeficiency virus and feline leukemia virus, should be performed. Additional screening tests for systemic involvement could include survey radiography and ultrasonography.

Cytology

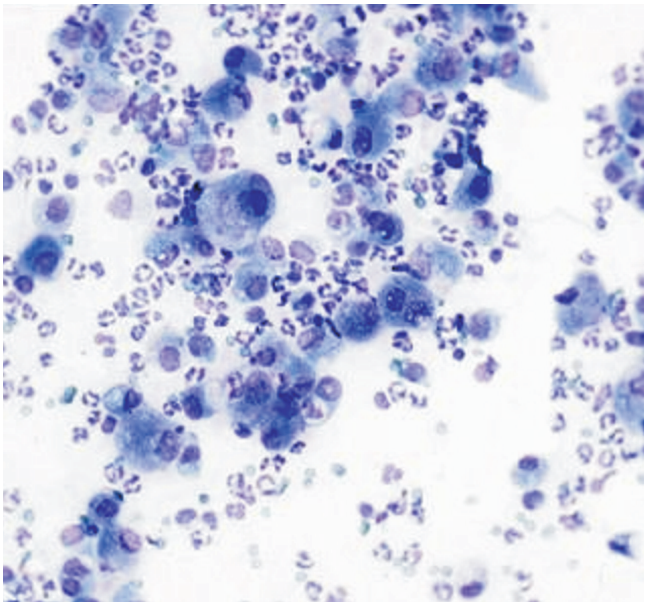
Material for cytological examination can be obtained by an impression smear, draining fistula, or fine-needle aspirate biopsy from nodules. Pyogranulomatous inflammation is characterized by a mixture of neutrophils and macrophages, whereas granulomatous inflammation is characterized by macrophages.

Organisms may be visible within the macrophages, within lipid vacuoles, or within giant cells in smears stained with a modified Wright's stain (Diff Quik) (Figure 28-8), or they may require Gram-staining or an acid-fast stain such as Ziehl-Neelsen stain. The absence of visible organisms on direct smears, or histology, does not rule out infectious causes.

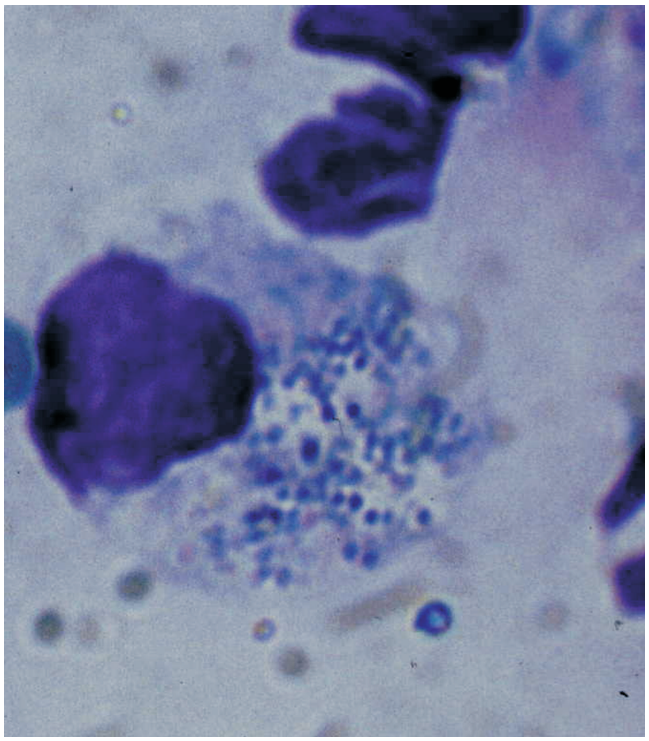
Tissue Biopsies

Tissue biopsies usually are submitted for histology and should be used for the culture of infectious organisms.

Histologically, these lesions produce nodular to diffuse dermatitis and/or panniculitis patterns composed of coalescing granulomas or pyogranulomas. The inflammatory cells are macrophages, neutrophils, and a small number of lymphocytes. The infectious organism may be visible in cytoplasmic vacuoles or within clear spaces surrounded by neutrophils and macrophages (Figure 28-9). In other cases, especially with actinobacillosis, *Arcanobacterium pyogenes* infection (actinomycosis), and staphylococcal infections, club-colonies consisting of a central core of organisms surrounded by radial array of eosinophilic material, referred to as the Splendore-Hoeppli reaction, may be evident.[35] The morphology of the organism, and special stains such as the Brown and Brenn's Gram tissue stain and modified acid-fast stains, give an indication of the causative organism and provide useful information for the microbiologist.



A



B

Figure 28-8. A, Pyogranulomatous inflammation with segmented neutrophils and large macrophages. **B**, Organisms within the cytoplasmic vacuoles, which were identified as *R. equi* on culture.

Identification of the organism on culture provides a definitive diagnosis. Many require specific culture media and aerobic or anaerobic conditions for growth. Because many organisms are intracellular or protected within a granuloma, they need to be released from the cells, or the granuloma, for culture. This is best achieved by grinding up the tissue sample before culture. The most common pitfall in identification of the causative organism in such cases is submitting a swab sample, because most likely this will culture contaminants.

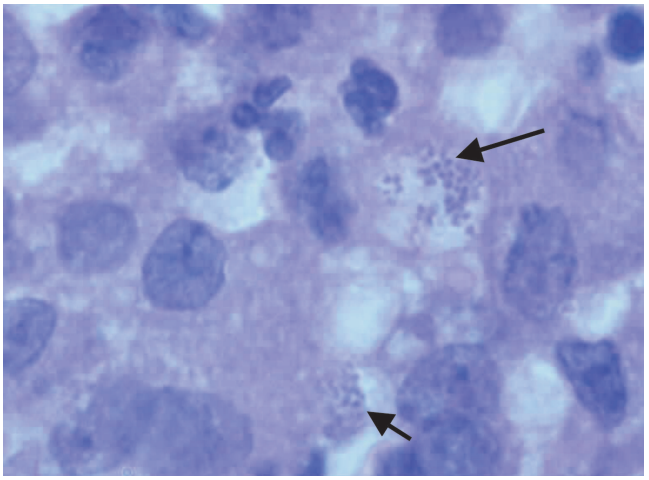


Figure 28-9. Presence of intracellular organisms within macrophages as seen on histology.

Treatment

Successful treatment depends on a number of different factors, which include the number and site of the lesions, the immune status of the cat, and the presence of systemic involvement. The prognosis in cats with widespread lesions, or with an underlying disease, is guarded.

Complete wide margin surgical excision of the infected tissue is the most successful treatment for single lesions. If widespread involvement occurs, surgical debulking together with long courses of antibiotics is recommended.

Empirical treatment with high doses of penicillins such as penicillin G, amoxicillin, and oxacillin are the drugs of choice for *Arcanobacterium pyogenes* infection (actinomycosis), nocardiosis, and dermatophilosis. However, the resistance patterns of organisms have changed with time and the advent of newer antibacterial agent therapy, based on sensitivity testing, is recommended (see Table 28-2). Treatment should be continued for at least 4 weeks beyond clinical cure.

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Chapter 29

Diagnosis and Management of Pemphigus Foliaceus

Sue Paterson

The pemphigus group of diseases is the most common of the autoimmune skin problems recognized in dogs and cats.[1] Five forms of pemphigus have been recognized in domestic pets: pemphigus foliaceus (PF), pemphigus erythematosus (PE), panepidermal pustular pemphigus (PEPP), pemphigus vulgaris (PV), and paraneoplastic pemphigus (PNP). Only PV, PE, and PF have been described in cats, to my knowledge. Although the first two disorders are rare, PF is a relatively common disease and has been reported to account for as high as 1 per cent of all cases in a busy dermatology clinic.[1]

ETIOLOGY AND PATHOGENESIS

The pathomechanism of PF in domestic species to date has been defined only in dogs. The antigens responsible are desmosomal glycoproteins of the cadherin group of intercellular adhesion molecules. The antigen targeted in the skin in PF in human beings and dogs is a 148 to 150 kD glycoprotein desmoglein 1 (Dsg1).[2-4] Desmogleins are associated with a desmosomal plaque protein called plakoglobin, which plays an important role in cellular adhesion. Autoantibodies binding to Dsg1 lead to loss of intercellular adhesion and epidermal damage. Work in dogs has shown that Dsg1 is located and expressed strongly in the superficial epidermis.[5] The same workers also have demonstrated that Dsg1 is expressed only weakly at mucocutaneous junctions and the oral mucosa. This is compared with desmoglein 3, the target protein in PV, which has a much deeper location and is expressed strongly at the latter sites. Therefore the distribution of lesions in PF and PV in dogs possibly results from the location of the target antigen. Lesions in PF are located superficially, and acantholysis occurs at the intragranular or subcorneal sites. Only rarely do lesions affect mucous membranes. Similar work has not been published on the target protein and its distribution in feline skin, although it is likely similar.

Canine PF presumably occurs in three forms[1]: spontaneous, drug-induced, and chronic. *Spontaneous PF* is seen most commonly in breeds such as the Akita and chow chow. In these cases, the strong breed predilection may indicate a genetic component of the disease. *Drug-induced PF* is seen classically in breeds such as the Doberman pinscher and can be seen at any age. *Chronic PF* is thought to be associated with cutaneous damage resulting from diseases such as longstanding allergy. Dogs with chronic PF typically are elderly. The last category is somewhat controversial because some dermatologists would argue this group also has had prolonged drug exposure. In my experience, dogs with chronic PF do not improve after complete and prolonged drug withdrawal, which suggests they are a separate category from drug-induced PF and may be a manifestation of drug-triggered PF.[6,7]

Strong breed predilections have not been noted in cats as in dogs.[1,11] In one study,[8] domestic short-haired cats accounted for approximately 60 per cent of all cases. However, many other breeds including orientals and long-haired and short-haired varieties were represented. Although this does not support a genetic component to PF in cats, two littermates also were included in the same study with identical clinical presentations, including types and distribution of lesions and response to therapy.

Several authors have reported drug-associated PF in cats.[9-11] Antibiotics, especially penicillins (e.g., amoxicillin[11] and ampicillin[10]) and sulfonamides,[11] have been implicated, in addition to cimetidine.[11] A recent review of 57 cases of feline PF also cited itraconazole, lime sulfur dip, methimazole, and ipodate as other drugs that may be implicated as potential triggers.[8] Eleven cats in the recent series of cases of PF reported by Preziosi, Goldschmidt, Greek, et al[8] had a previous history of skin disease. Dermatological diseases considered unrelated to the PF included otitis externa, acne, and pyoderma. However, in two cases, a previous longstanding history of allergic disease was reported, which could suggest that chronic skin inflammation may be a trigger. One of the cases of PF thought to be induced by ipodate required therapy even after adequate drug withdrawal, which suggests this may have been a drug-induced problem.

No age predisposition has been noted in cats with PF.[1,2,11-15] The largest series of case reports published to date[8] showed the median age of onset was 5 years, with a range of less than 1 to 17 years. The same report showed no evidence of a sex predilection, with 52.6 per cent of affected cats being female

and 47.4 per cent male. No seasonal or environmental risk factors have been identified in cats with PF.

CLINICAL SIGNS

Feline PF starts with lesions most commonly on the head,[1,7,11-13] especially on the pinna,[8] although the nose, chin, and periocular areas often are involved. Lesions may remain localized or can become generalized. Localized lesions are seen most commonly on the bridge of the nose, muzzle, nasal planum, periocular region, pinnae, area around the nipples, footpads, and nail beds.[15] Griffin[12] suggests that paronychial and nipple involvement are common manifestations. In a report by Preziosi, Goldschmidt, Greek, et al,[8] almost 80 per cent had involvement of the head; the pinnae were involved in about 70 per cent of cats (Figure 29-1). Facial signs appear as primary pustular lesions that progress rapidly to crusted papules (Figure 29-2). The medial aspect of the ear pinna appears to be a common site for such lesions. Crusting can occur on the planum nasale, and chronic lesions at this site may become depigmented. Lesions tend to be bilaterally symmetrical.

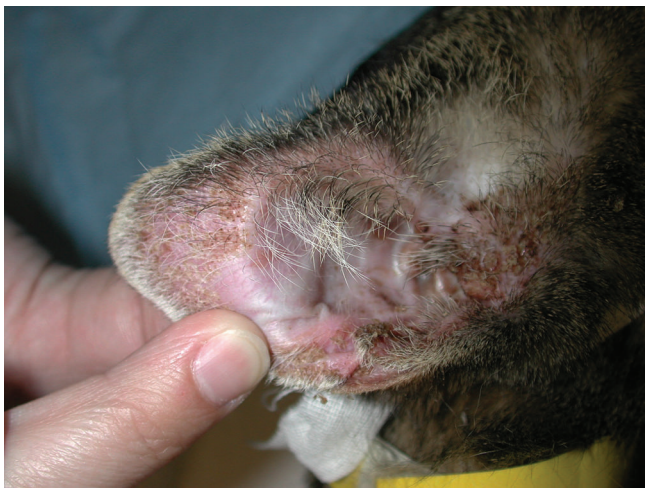

Figure 29-1. Crusting on ear tips of cat with pemphigus foliaceus.

Figure 29-2. Facial lesions of cat with pemphigus foliaceus.

Sterile paronychia affecting multiple toes and feet also is described commonly[1,7,11-15] (Figure 29-3). The discharge, which typically is thick, caseous, and sterile, is referred to colloquially by some dermatologists as "Philadelphia feet." These lesions are useful sources of material for diagnostic cytology. The nail folds also may be swollen and eroded.[15] Although marked changes are seen around the nail beds, nail changes seem to be rare; onychomadesis has been reported by only one author.[11] Pad lesions can occur concurrently with nail fold disease. Footpad hyperkeratosis is an uncommon finding in my experience. However, the footpad lesions can include pustules, crusting, scaling, and pitting. Pustules at this site tend to be large and fluctuant, but usually are transient because of their superficial nature. Often the clinician is presented only with the tattered remnants of the ruptured pustule. Primary lesions generally are difficult to find in feline PF. In many cases this is because of the suppressive effects of prior steroid therapy at the time of biopsy. However, lesions consist predominantly of thick adherent crusts with associated scale and alopecia.

Although many cats present with localized disease, PF can generalize to involve the dorsum and ventrum. A recent report suggested that almost 50 per cent of animals had dorsal lesions and close to 40 per cent had involvement of the ventrum.[8] Pustules can be grouped, which gives the appearance of large crusted plaque. The lesions may occur in a polycyclic or arciform pattern.[11,15] The ability to "slip" the skin at the periphery of lesions, the so-called Nikolsky sign, may be present in some cases.

Affected cats may present with superficial spreading lesions without any obvious primary pustules when acantholysis is confined to the follicular sheaths and not the interfollicular spaces. These lesions present typically as an expanding area of alopecia with peripheral crust. Hairs can be epilated easily from the periphery of the lesions, suggestive of a follicular insult. Cats with PF exhibit mild to moderate signs of pruritus.

Systemic signs are less common and generally affect less than 50 per cent of all cases.[8] When present, they include lethargy, pyrexia, anorexia, weight loss, and lymphadenopathy. Affected cats may manifest signs of lameness when footpads are involved.

Figure 29-3. Crusting and ulceration around multiple nails in cat with pemphigus foliaceus.

DIFFERENTIAL DIAGNOSES

The differential diagnoses for feline pustular/papular lesions are numerous and should include dermatophytosis, demodicosis, notoedric mange, leishmaniasis, bacterial folliculitis, discoid and systemic lupus, and cutaneous adverse drug reactions. When lesions are localized to the face, additional differential diagnoses include allergy, especially atopy and food intolerance, and cowpox infection.

The major differential diagnoses for paronychial disease include infection and neoplasia. Staphylococcal infection of the nail beds may be seen in allergic cats, particularly those with atopic dermatitis. Immunocompromised cats, especially those with feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), and feline infectious peritonitis (FIP) infections, also are susceptible to infection at this anatomical site. Yeast infection caused by *Malassezia* spp. can affect the skin around the nail beds, although this also often occurs as a secondary finding in immunosuppressed cats. The most common neoplastic lesions to affect the toes are metastatic bronchogenic carcinoma and squamous cell carcinoma of the lungs.

DIAGNOSIS

Establishment of a diagnosis is imperative in all cases of PF in cats. Ideally, diagnostic tests should be undertaken before initiation of any immune-modulating therapy. In one report,[8] 17 of 57 affected cats were receiving some form of corticosteroid at the time of biopsy. This resulted in a significant reduction in the proportion of diagnostic samples compared with those cats that had not received corticosteroids. A diagnosis should be based on clinical history, physical examination, cytology, and histopathology. Other diagnostic tests that should be performed as part of a more general evaluation and to exclude other differential diagnoses include fungal culture, bacteriology, skin scrapings, hair plucks, and impression smears. Diagnostic tests that may be useful in long-term management of the patient, especially when considering side effects of medication and the cat's ability to tolerate medication, include complete blood counts, biochemistry profiles, and FeLV and FIV testing. Immunofluorescence, immunohistochemical testing, and demonstration of the antigen being targeted (Dsg1) also can be performed but tend to be available only at teaching and research facilities. I do not consider response to therapy an appropriate diagnostic criterion, especially when a diagnosis commits many affected cats to a lifetime of immunosuppressive therapy.

Blood counts reveal a variety of clinical findings. Leukocytosis, neutrophilia, lymphopenia, monocytosis, eosinophilia, basophilia, and mild normocytic normochromic anemia have been recorded.[8] Biochemistry in PF rarely reveals anything other than mild, nonspecific signs.

Cytology is an essential clue in the diagnosis of PF. When possible, cytology should be taken from primary pustular lesions. However, when these are rare, those pustules present should be preserved for histopathology. However, much useful information can be gleaned from impression smears of papules and from moist crusts. Useful diagnostic specimens often can be obtained from moist lesions in the inner pinnae. Cytology of an intact pustule can be obtained by puncturing the lesion using a fine needle and then expressing the contents carefully onto a clean microscope slide. Care should be taken not to smear the sample because this damages cellular integrity. Not all of the slides should be heat-fixed in suspect cases, because this may affect cell morphology. After heat-fixing some of the slides, a variety of stains may be used, including rapid staining techniques such as Diff-Quik (Dade Behring, Inc.) or Rapistain (DiacheM), which are useful for the practice laboratory, or Giemsa and methylene blue.[16]

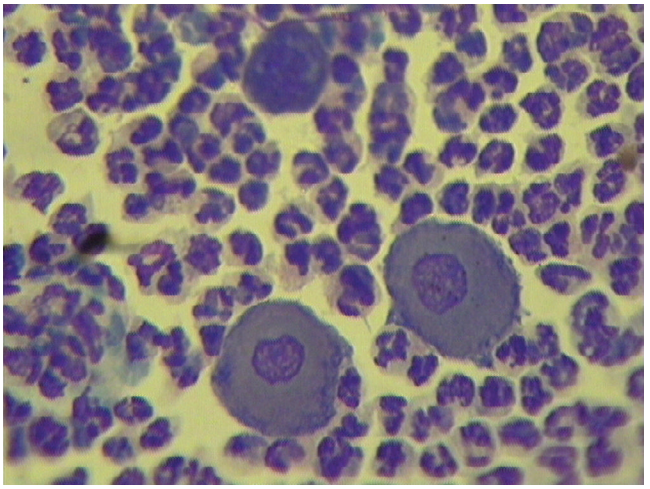

Figure 29-4. Cytology of pemphigus foliaceus showing typical acanthocytes. (Courtesy B. Pickavance.)

In a simple case uncomplicated with secondary infection, cytology reveals nondegenerative neutrophils, eosinophils, and few to many acantholytic keratinocytes (acanthocytes) (Figure 29-4). These are the nucleated epithelial cells released from the stratum spinosum or granulosum following desmosomal damage. When secondary bacterial infection is present, bacteria are visible in addition to acanthocytes, and neutrophils tend to be more degenerate. Acanthocytes may be produced in other diseases, such as bacterial folliculitis and dermatophytosis[17]; therefore, PF complicated by secondary infection can produce a difficult diagnostic dilemma. In such cases, many dermatologists would advocate conservative therapy with an appropriate antistaphylococcal antibiotic (e.g., cephalexin 20-30 mg/kg PO q12h) before reassessing the case after 2 to 3 weeks to repeat cytology.

Biopsy remains the best diagnostic aid. Multiple biopsies, when possible from primary lesions, provide the most useful information. When primary lesions cannot be identified, secondary lesions such as papules and crusts can be sampled. Although these lesions still may contain acanthocytes, they are not as reliable as pustules. Alternatively, clipping hair over lesional skin and hospitalizing the cat is a possibility, checking it hourly to see if lesions develop that are suitable for biopsy.

Sampling technique also is important. A sharp, adequate-size (6-mm) biopsy punch should be used to ensure the whole lesion is contained within it. Gentle collection, when possible, prevents rupture of the pustule. In some cases, intact pustules can be harvested only by elliptical biopsy. Samples should be preserved in 10 per cent neutral buffered formalin and sent to a veterinary histopathologist with expertise in dermatohistopathology. Biopsies normally are considered to be diagnostic of PF when based on the criteria defined for dogs.[18] Essential criteria for diagnosis of PF include evidence of acantholytic cells within a pustule or degenerating pustules along with granulocytic cells.

In one feline study,[8] analysis of pustule contents in 208 biopsies of PF revealed the predominant granulocytic cell type to be the neutrophil. Although eosinophils were present in many biopsies, they were not considered the main cell type in any case. Pustules that span several hair follicles in haired samples also are important diagnostic criteria. Pustules should be subcorneal or intragranular. Other factors considered helpful but not crucial to make a diagnosis include the presence of rafts of acantholytic cells clinging to the overlying stratum corneum, so-called "cling-ons." In the same large study of 57 cases of PF in cats,[8] 21 per cent of samples contained these adherent acantholytic cells. The follicular outer root sheath may be included in the acantholytic and pustular process. Samples considered suggestive of PF are pustules with a cornified base that span more than two hair follicles and have five or fewer acantholytic cells with no active acantholysis. Steroid therapy at the time of biopsy does not decrease the number of acantholytic cells or number of rafts of acantholytic cells seen in biopsies, but does decrease significantly the number of biopsies that contained adequate diagnostic criteria.[8]

Detection of pemphigus antibodies by direct immunofluorescence and immunohistochemistry may be helpful as adjunct tests. However, the presence of both false-negative and false-positive results for these procedures questions their diagnostic sensitivity. True positive results for both direct immunofluorescence and immunohistochemical testing in PF demonstrate the presence of immunoglobulins (usually IgG, less commonly IgM and IgA) in addition to complement at intercellular sites in the upper epidermal layers.[19] Unfortunately, false-positive results can occur because immunoglobulin and complement deposition can occur in the skin as a result of tissue damage in a wide range of inflammatory skin conditions. False-negative results usually are associated with steroid administration, although improper fixation of the sample or poor sample collection can produce similar results.[20] Although true-positive results are achieved more commonly with immunohistochemical (immunoperoxidase) staining, this technique also tends to produce significantly more false-positive reactions. Therefore submission of samples for routine histopathology always should take precedent over submission of samples for immunological testing.

TREATMENT

The choice of drugs for the therapy of PF depends on the initial presentation. When lesions are localized, therapy can be implemented with topical drugs. These cats may or may not need systemic therapy at a later date. Systemic therapy is more appropriate when clinical signs are widespread or progress to become generalized. Emerging evidence demonstrates that lifelong therapy may not be necessary in all cats with PF. However, clients should be warned that this may be the exception rather than the rule and to expect that their cat will need lifelong therapy.

Topical Therapy Options for Cats with Localized Lesions

Glucocorticoids

A potent topical preparation should be used to induce clinical remission of signs (resolution of signs and no further development of new lesions), followed by a change to a less potent glucocorticoid. In most cases "maximum" response usually occurs within 14 days. Suitable topical glucocorticoids for initial therapy include 0.1 per cent amcinonide cream (Cyclocort, Lederle), 0.05 per cent fluocinonide cream (Lidex, Dermik), 0.015 per cent triamcinolone cream (GENESIS, Virbac),[21] 0.1 per cent betamethasone valerate gel (Fuciderm, Leo Laboratories), and 0.5 per cent betamethasone valerate cream (Vetsovate cream, Schering-Plough Animal Health). When a good clinical response is not achieved within 14 days with topical therapy, I would advocate a change to a less potent corticosteroid to prevent side effects and the introduction of systemic therapy. Prolonged use of potent topical glucocorticoids produces localized changes in the skin at the site of application, such as atrophy and alopecia. They also are absorbed systemically by percutaneous absorption or by the cat's grooming activity, which potentially can produce signs of iatrogenic hyperadrenocorticism.

Cyclosporine and Tacrolimus

I do not recommend use of these drugs in cats because of the potential for toxicity and/or lack of efficacy. Topical tacrolimus has been used with some success in dogs.[22] However, because of the greater toxicity of tacrolimus and the cat's inherent tendency to ingest topical medication, it is not recommended for use in cats with PF.

Systemic Therapy

Glucocorticoids

Glucocorticoids are recognized as the first drug of choice for PF in cats.* Most commonly, prednisolone or prednisone is used at immunosuppressive doses of 4.4 to 6.6 mg/kg PO q24h. This dose rate is administered for 14 days and then tapered over the next 28 days to the lowest possible alternate-day dosage. Whenever possible, this maintenance dose should be 1.1 to 2.2 mg/kg q48h. Some authors suggest that methylprednisolone is a better first-line drug used at the same dose rate as prednisolone because it produces fewer mineralocorticoid side effects.[21] Triamcinolone or dexamethasone may be used if oral prednisolone, prednisone, or methylprednisolone are not effective. Preziosi reported that triamcinolone was significantly more effective in inducing remission ($P < 0.023$) and was associated with fewer side effects than prednisone/leukeran ($P < 0.044$); however, no difference was noted from prednisone alone with regard to side effects. Because triamcinolone and dexamethasone are 6 to10 times more potent than prednisolone, they should be used with care. They produce suppression of the hypothalamic-pituitary-adrenal axis for 24 to 48 hours and should be administered every 72 hours whenever possible. Induction and maintenance doses are detailed in Table 29-1 and monitoring of drug therapy is detailed in Table 29-2.

Side effects associated with glucocorticoid therapy are numerous. Systemic signs include poor hair coat, polyuria, polydipsia, polyphagia, weight gain, behavioral changes, and risk of infection.[21] Bladder infections appear to be particularly common, and many authors advocate urinalysis and urine culture twice yearly. Diabetes mellitus may occur when more potent steroids are used, although this may occur even with oral

*References 1,7,11,13-15,23.

Table 29-1 | **Drugs Used Most Commonly for Therapy for Feline Pemphigus Foliaceus**

	DRUGS	INDUCTION THERAPY	MAINTENANCE THERAPY
Glucocorticoids	Prednisolone	4.4-6.6 mg/kg q24h for 14 days	1.1-2.2 mg/kg q48h
	Methylprednisolone	4.4-6.6 mg/kg q24h for 14 days	1.1-2.2 mg/kg q48h
	Triamcinolone	0.2-0.6 mg/kg q24h for 14 days	0.1-0.2 mg/kg q48-72h
	Dexamethasone	0.2-0.4 mg/kg q24h for 14 days	0.05-0.1 mg/kg q48-72h
Chlorambucil		0.1-0.2 mg/kg q24-48h	0.1-0.2 mg/kg q24-48h
Gold salts	Auranofin	0.1-0.2 mg/kg daily	0.1-0.2 mg/kg at lowest possible frequency
	Aurothiomalate or aurothioglucose	1 mg/kg q7d	1 mg/kg q30-60d

Table 29-2 | **Monitoring of Drug Therapy in Feline Pemphigus Foliaceus**

DRUGS	MONITORING
Glucocorticoids	Twice yearly blood counts, chemistry profiles, urinalysis, and urine cultures
Chlorambucil	Routine hematology (including platelet count), liver function tests every 2-4 weeks for 2 months, then 3-4 times yearly
Gold salts	Routine hematology (including platelet counts) and biochemistry every 2-3 weeks for 4 months, then 2-4 times yearly

prednisone used every 48 hours. Skin infections, especially dermatophytosis, *Malassezia* infections, and demodicosis, may be seen with chronic steroid usage. I always insist on personal reassessment of cats by the clinician when ongoing cases flare because of the possible development of these opportunistic pathogens.

An alternative or concurrent immunosuppressive drug should be introduced when glucocorticoid treatment alone fails to produce remission or leads to unacceptable side effects. Some clinicians prefer to use combination therapy as an initial treatment strategy.

Azathioprine

Azathioprine is used commonly in dogs for the therapy of PF. However, because of its profound myelosuppressive effects and risk of fatal reactions in cats, it is *not* recommended for use in that species.

Chlorambucil

Chlorambucil is an alkylating agent that functions by affecting the cross-linkage of DNA. It is considered less toxic and slower acting than other alkylating agents and is used most commonly to replace glucocorticoids or act in a steroid-sparing capacity for therapy of feline PF.[1,21,23] The oral dose rate is 0.1 to 0.2 mg/kg q24h or q48h. Because of its slow onset of action, a lag phase of 3 to 6 weeks normally is observed before benefits are seen. I start this drug in combination with glucocorticoids and do not attempt to decrease glucocorticoid doses (unless unacceptable side effects were noted) until at least 4 weeks into therapy. Chlorambucil replaces steroid therapy in many cases and can be the sole agent used, but will act, at worst, in an excellent steroid-sparing capacity. Alternating the drugs limits gastrointestinal irritation. Chlorambucil and glucocorticoids are given on alternating days.

The most important side effect of therapy is myelosuppression. Consequently, patients should be monitored with routine hematology, including a platelet count, every 2 to 4 weeks in the initial 2 months of therapy. Once the cat's tolerance of the drug has been assessed, monitoring may be decreased to three to four times a year. When bone marrow suppression occurs, the chlorambucil should be withdrawn until parameters return to normal; it then may be reintroduced carefully at a lower dose rate. Hepatotoxicity also has been noted in addition to anorexia, vomiting, and diarrhea.

Gold Salts

Gold salts (chrysotherapy) can be used in cats with PF alone or in a steroid-sparing capacity. They are available as oral (auranofin) and intramuscular (aurothiomalate or aurothioglucose) formulations. The intramuscular form generally is accepted as being the most effective, although aurothioglucose is no longer widely available.[21] The mechanism of action of gold is unknown, but it is recognized as having both immune-modulating and antiinflammatory effects.[23] In cats, the intramuscular formulation is given at a dose of 1 mg/kg weekly until remission occurs, which is usually 6 to 12 weeks, given the lag phase with gold therapy. Therapy then can be decreased to maintenance dosing given every 2 weeks for 2 to 3 months, then once every 1 to 2 months. Few references detail the use of oral gold. The reported dose rate is 0.1 to 0.2 mg/kg q24h.[15] About 25 per cent of glucocorticoid-resistant cats respond to chrysotherapy.[11]

Side effects with gold therapy include bone marrow suppression, oral ulcers, and glomerulonephropathy. Gold has been implicated in cutaneous drug eruptions. Monitoring should be undertaken with routine hematology (including platelet counts) and biochemistry every 2 to 3 weeks for the first 4 months of therapy, and then two to four times yearly.

Other Less Common Systemic Drugs

Cyclosporine

Cyclosporine has been reported to have little benefit when used systemically to treat PF in dogs and cats. A dose rate of 20 mg/kg PO q24h is recommended.[15] If benefits are seen, the dose can be tapered to 10 mg/kg q48h. Cyclosporine can be used in conjunction with glucocorticoids. Side effects include diarrhea and vomiting.

Cyclophosphamide

Cyclophosphamide is another alkylating agent. It is very potent and, in my opinion, has no advantages over chlorambucil in cats. Its use in cats cannot be recommended because of its potential to cause severe hemorrhagic cystitis.

Doxycycline/Niacinamide

Anecdotal reports declare that doxycycline may act as an immunomodulatory drug in cats.[15] Niacinamide inhibits mast cell degranulation and phosphodiesterase. Doxycycline may be tried at a dose rate of 20 mg/kg PO daily with or without niacinamide.[15] Niacinamide is administered at a dose of 250 mg PO q8h.

Dapsone

Cats appear very sensitive to the effects of dapsone and commonly develop hemolytic anemia and neurotoxicity. Its use probably is best avoided in this species.

Mycophenolate Mofetil

Mycophenolate mofetil is a new drug that inhibits de novo purine synthesis. Studies on the use of this drug in dogs with autoimmune skin disease have shown promise both as a steroid-sparing drug and as sole therapy.[24]

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Chapter 30

Controversial and Emerging Diseases

Joan R. Rest

In the past decade, new patterns of dermatological disease have been recognized, and the prevalence of other diseases has changed. Increased use of well-established techniques such as histopathology has helped to characterize the former, with advances in molecular techniques and immunology enabling us to understand causes and mechanisms. Epidemiological studies have shown that the prevalence of some diseases in cats corresponds with variations in rodent populations.

The diseases highlighted in this chapter are those seen by a dermatopathologist and for which histopathology often is a useful diagnostic tool. They are in two main groups: infections and syndromes of unknown cause with an immunological component.

Many of these diseases are rare but must be recognized for prognostic or treatment reasons, or because they have zoonotic potential. Some of the concepts discussed are controversial either because minimal published, peer-reviewed literature exists or because underlying assumptions need challenging. Inevitably, some hypotheses may prove erroneous. In the next few years, a better understanding of the immune mechanisms and causes should emerge and new infections, particularly those transmitted by vectors or associated with protozoa, will be recognized.

DISEASES OF UNKNOWN CAUSE

Plasma Cell Pododermatitis

This syndrome occurs worldwide but is rare.[1-7] To date, no breed, age, or sex predilection has been shown. Two studies have described an association with feline immunodeficiency virus (FIV) in approximately half the cats studied[6,8]; however, this correlation has not been confirmed in other studies and the prevalence of FIV is changing. Seasonal occurrence of some cases has been noted[1] but has not been confirmed in larger studies. In my experience, clustering of cases may occur, although this could be a random effect.

The pathogenesis is uncertain but hypergammaglobulinemia is a consistent feature.[9] The disease therefore is considered to have an immune-mediated component. Additional features such as glomerulonephritis, leukoclastic vasculitis,[10] and plasma cell stomatitis have been described in small numbers of affected cats and attributed to a common syndrome.[11] However, because these changes are not present in all cats, this remains unproven. Plasmacytic stomatitis, for example, is a common reaction pattern and not a disease entity. A recent clinical case with which the author was associated was in a cat with lymphocytic mural folliculitis (Figure 30-1). Swollen pads also have been recorded in association with cutaneous lymphocytosis,[12] which possibly indicates that the feline footpad represents an immunological target similar to sebaceous glands.

The lesions start as single or multiple pad swellings (Figures 30-2 and 30-3). The swollen pads often look purple and cross-hatched with pale striae and feel spongy. Bleeding sometimes is a feature.[1,5] The most common reason for presentation is lameness. Reports of pain are variable and it is often absent in chronic, ulcerated cases. Pain may be related to pressure by the physical swelling rather than the presence of a primary agent.

The histopathological change usually is a dense infiltrate of plasma cells (Figure 30-4) with smaller numbers of lymphocytes and macrophages. Neutrophils often are perivascular or adjacent to ulcerations. Guaguere and Prelaud[6] noted that many affected cats had granulomatous rather than plasma cell–rich lesions. I have found mycobacteria in two cases (Figure 30-5), although other investigators in other areas have recorded negative results for infectious agents.[13] The variable histopathology and associations with disease in other organs suggest footpad swelling may occur occasionally in a variety of aberrant host immune responses. This implies that the clinical syndrome is not a single disease but a reaction pattern as suggested originally by Guaguere and Prelaud.[6] Infections (viruses and mycobacteria) and hypersensitivity reactions are possible primary factors.

A few cases have been treated surgically.[1,6,14,15] Most have been treated medically with immunomodulatory drugs* because an aberrant immune reaction has been considered to be, at least in part, responsible for ongoing disease. These have included vitamin E, corticosteroids, and most recently

*References 1,3,5-7,10,14,16.

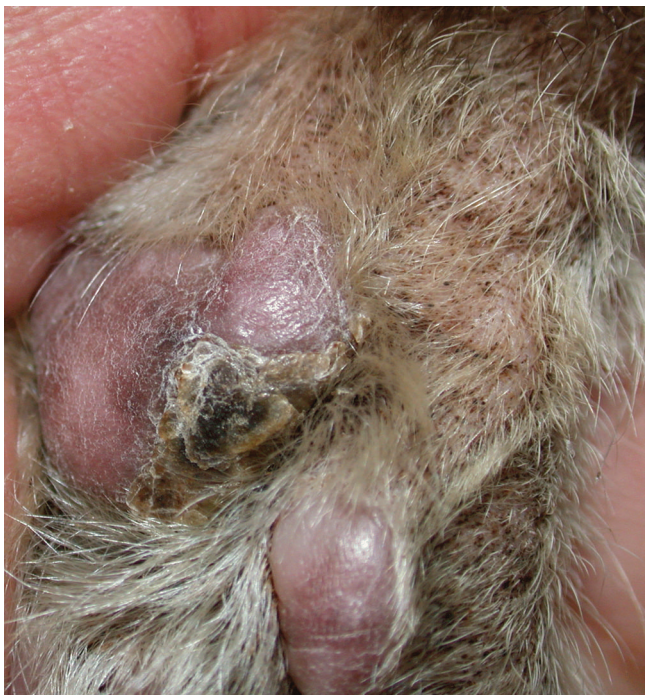

Figure 30-1. Swollen footpads of a cat with lymphocytic mural folliculitis. (Courtesy A. Patel.)

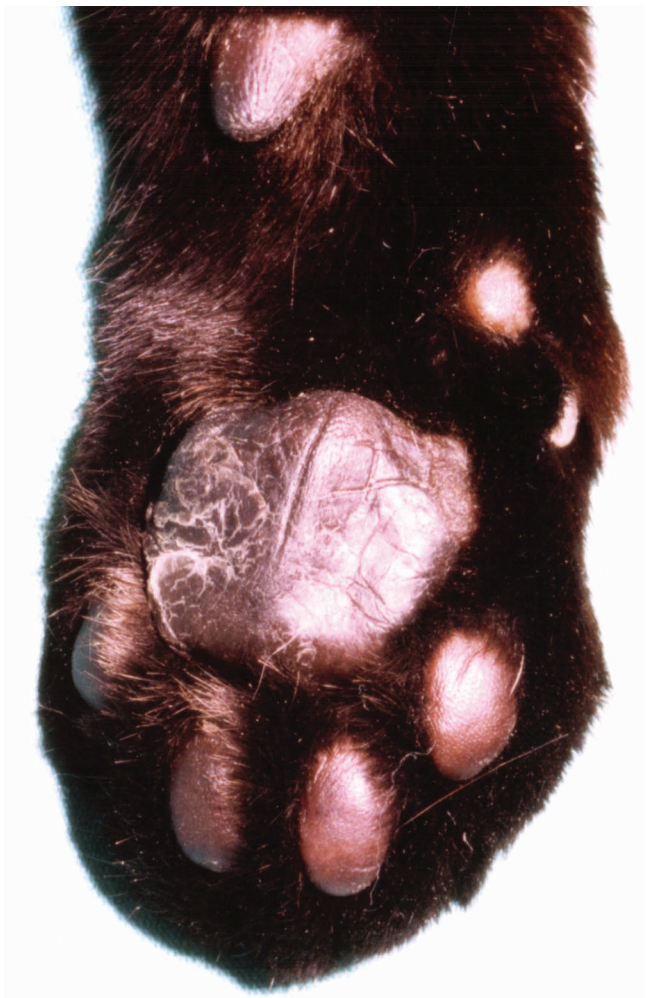

Figure 30-2. Plasma cell pododermatitis. Swollen, greyish-purple pad cross-hatched with pale striae. (Courtesy S. van Poucke.)

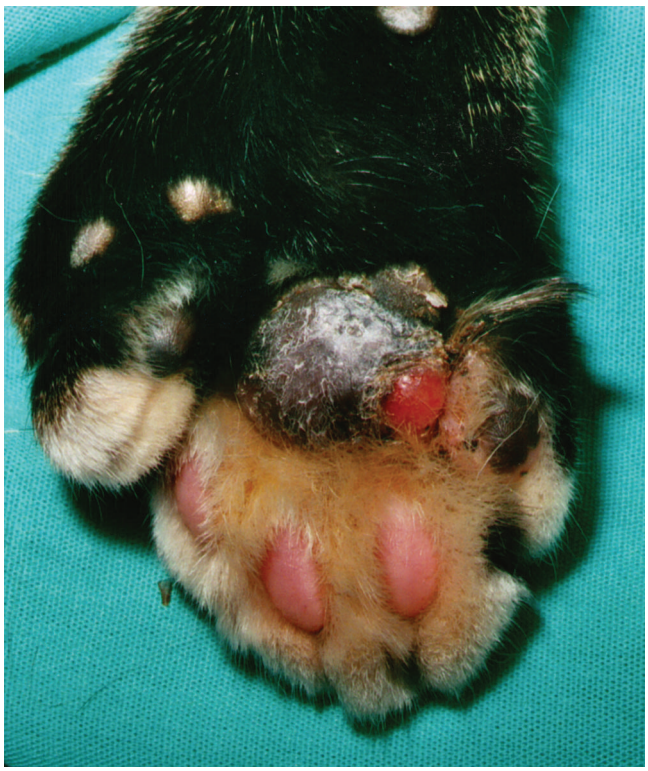

Figure 30-3. Plasma cell pododermatitis. Swollen pad with ulceration. Note polydactyly. (Courtesy S. van Poucke.)

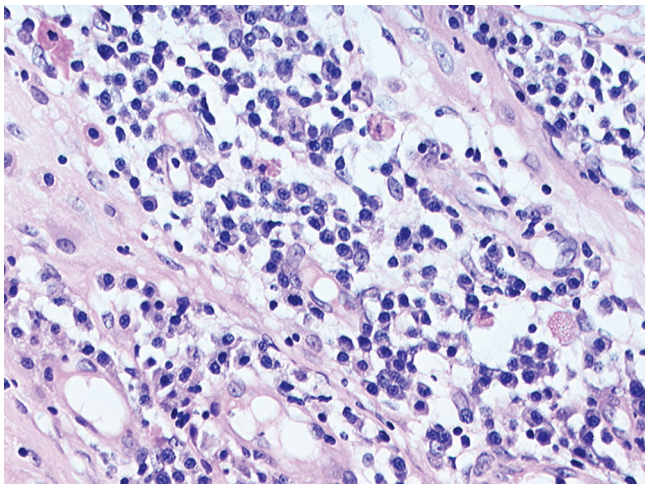

Figure 30-4. Plasma cell pododermatitis. Classical histopathology with a dense infiltrate of predominantly plasma cells with pink-staining Russell bodies. (H&E ×100.)

doxycycline (25 mg/kg PO daily for 3 to 8 weeks). The last drug was used in the largest series, with full remission in 35 per cent and partial remission in 53 per cent.[16] However, as in other studies,[1] some cats (4 out of 17) resolved spontaneously in a few months. Because plasma cell pododermatitis appears to be a clinical syndrome with multiple etiologies, spontaneous resolution or the outcome of treatment probably depends on the primary cause and whether it can be eliminated, in addition to halting the host reaction that causes the clinical swelling. The use of PCR techniques and better understanding of the feline immune system may enable us to understand this syndrome better.

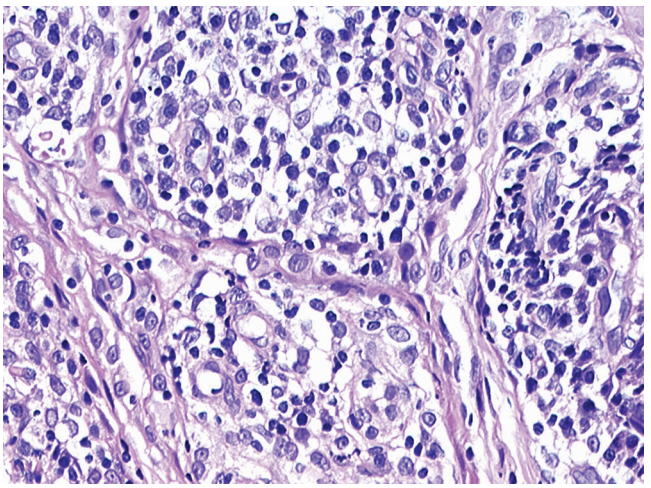

Figure 30-5. Plasma cell pododermatitis. Granulomatous infiltrate with nodular form and macrophages and lymphocytes predominating in the infiltrate. (H&E ×100.)

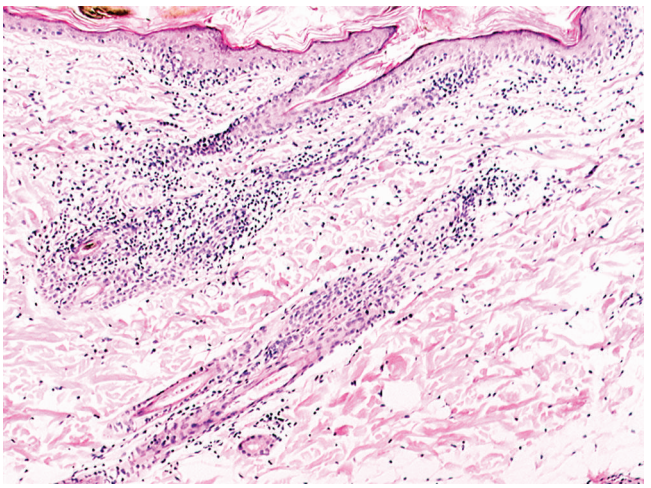

Figure 30-7. Lymphocytic mural folliculitis. Histopathology showing infiltration of the follicular wall by lymphocytes, loss of sebaceous glands, and follicular destruction. (H&E ×100.)

Figure 30-6. Lymphocytic mural folliculitis. Clinically severe case with scaling and alopecia. (Courtesy A. Patel.)

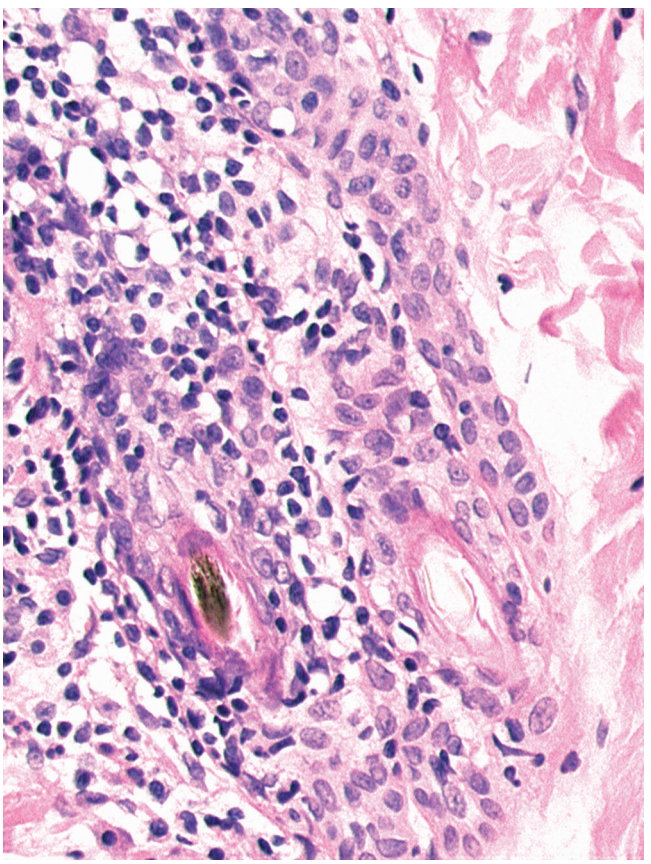

Figure 30-8. Lymphocytic mural folliculitis. Higher-power view of Figure 30-7. Histopathology showing infiltration of the follicular wall by lymphocytes and follicular destruction. (H&E ×400.)

Feline Lymphocytic Mural Folliculitis (Interface Isthmus Folliculitis, Pseudopelade)

Feline lymphocytic mural folliculitis is a poorly defined pathological entity that occurs worldwide. The literature on this rare condition is sparse. Feline sebaceous adenitis and mural folliculitis merge and are not distinguishable. Coexisting autoimmune conditions are said to exist in some cases. In one case, lymphocytic enteritis associated with diet was described,[17] seasonal incidence has been recorded in another with concomitant eosinophilia,[18] and I noted swollen foot pads in one case (see Figure 30-1).

Clinically severe cases present as alopecia or crusting or scaling disease (Figure 30-6). Histologically, the condition is characterized by infiltration of the follicular wall by lymphocytes (Figures 30-7 and 30-8) sometimes with pyogranulomatous inflammation of sebaceous glands and, in severe cases, follicular destruction.

Clinically mild cases probably are a form of allergic dermatitis with T-lymphocytes rather than eosinophils as the effector cell. They may be present within the follicular root sheath because the cats are plucking their hairs. These mild cases tend to recover or respond to the usual treatments for "miliary

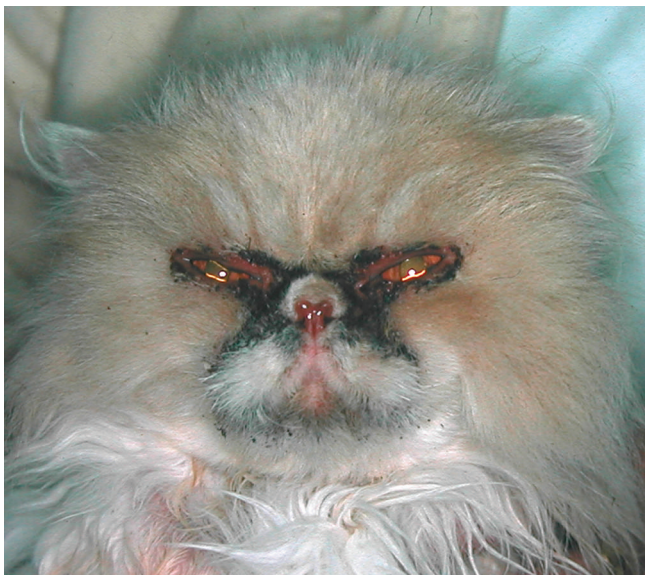

Figure 30-9. Idiopathic facial dermatitis. Persian cat with symmetrical periocular and facial "butterfly-shaped" sebum-rich black exudate. (Courtesy R. Bond, copyright Veterinary Dermatology, Blackwell Publishing.)

dermatitis." Whether the mild and severe forms of the condition are related is unclear. Lymphocytic mural follicular infiltrates have been recorded as a response to dermatophytes, and in reactions to *Demodex* mites, lupus erythematosus, and erythema multiforme.[19]

One group of cases was associated with follicular mucinosis, and three of seven affected cats were FIV-positive.[20] Some severe cases have been associated with autoimmunity,[21] but whether this is true of all cases is uncertain. Some cases may be early epitheliotropic lymphoma, but this may be a diagnostic problem rather than progression. I have seen severe cases with underlying neoplasia and a similar numbers of cases responding to antibiotics alone (two on at least three occasions with relapse on cessation of treatment). One was treated with ampicillin and the other with amoxicillin/clavulanic acid. I also have seen the syndrome in a diabetic cat and after a topical treatment (presumed to be a reaction to the therapy). Treatment by immunomodulation has been attempted[21] as has change in diet.[17]

Like plasma cell pododermatitis, feline lymphocytic mural folliculitis appears to be a pathological reaction pattern rather than a single clinical disease. Triggers need to be better identified and distinguished to assist in prognosis and treatment. In the light of our current knowledge, severe cases should have a guarded prognosis.

Idiopathic Facial Dermatitis of Persian Cats

A disease of Persian cats was recognized in the 1990s, and 13 cases were analyzed retrospectively and their features recorded.[22] The striking clinical feature was the deposition of black, waxy material with symmetrical facial distribution (Figure 30-9). Erythema and excoriation were present to varying degrees. Ceruminous otitis was seen in seven of the cases, and five had enlarged submandibular lymph nodes. Histopathology showed features that included crusted black sebaceous gland secretion on the surface, marked acanthosis of the surface epithelium with basal vacuolation, and dyskeratosis, mixed, interface, dermal inflammation with eosinophil exocytosis, and sebaceous gland enlargement (Figures 30-10 and 30-11). *Malassezia pachydermatis* yeasts and various bacteria were isolated from some cats, but in no case was antimicrobial therapy curative. The response to glucocorticoids was variable and often poor, and no satisfactory therapeutic regimen has been identified. As the condition is confined to this breed and presented at a relatively early age (10 months to 10 years with a median of 2½ years), a genetic basis is possible.

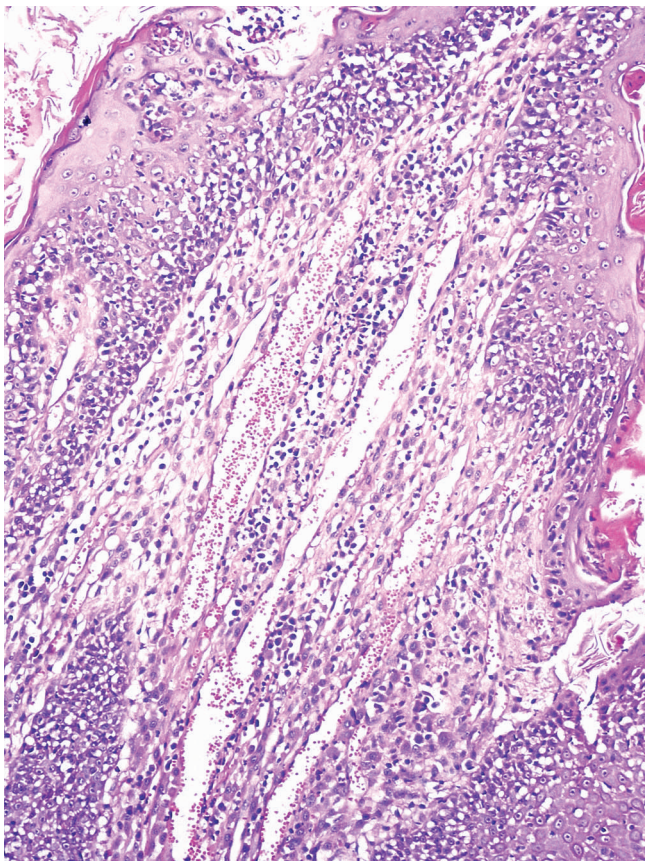

Figure 30-10. Idiopathic facial dermatitis. Interface dermatitis affecting the acanthotic, crusted surface epithelium and follicles. (H&E ×100.)

This is a feline dermatological condition with an eosinophilic reaction, which is not due to hypersensitivity. Investigation of both the immune reactions involved and the underlying genetics of the Persian breed may help us to understand this condition.

Chondritis

Auricular chondritis ("floppy ears") is a rare disease, with only two peer-reviewed recorded cases in cats.[23,24] Although a paucity of peer-reviewed publications exists, continuing education seminars on feline dermatology suggest anecdotally that it may be more common than reported. Inflammation does affect the dermis but is mainly around and within the cartilage. This induces lysosomal enzyme release from chondrocytes, damaging the integrity of the cartilage matrix. The cartilage reacts by producing new growth, often deformed (Figures 30-12 and 30-13). The disease appears to be both relapsing and multicentric. Biopsies show deformed, hyper-

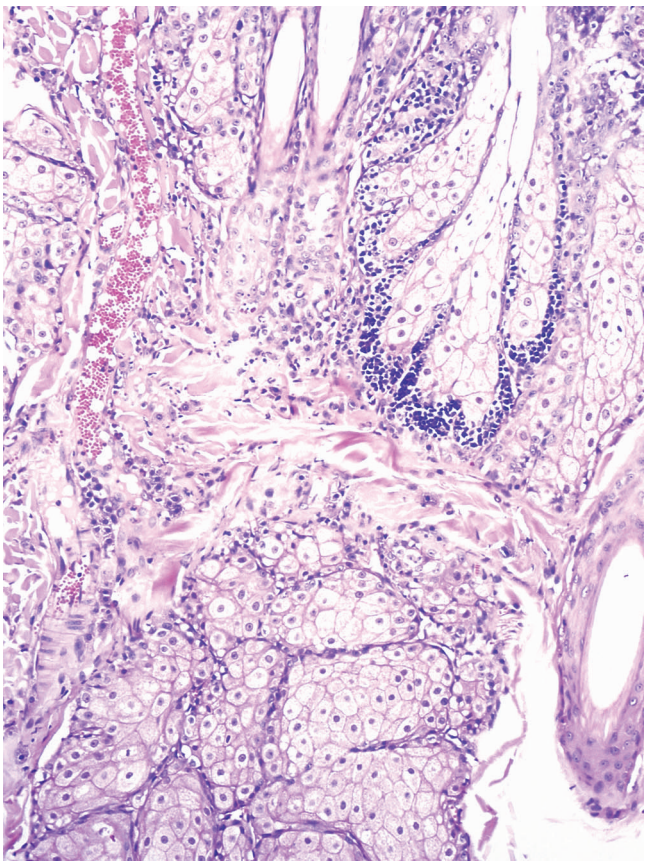

Figure 30-11. Idiopathic facial dermatitis. Enlarged sebaceous glands with periglandular lymphocytic infiltrates. (H&E ×100.)

Figure 30-12. Polychondritis. Cat with bilateral distortion of the pinnae. (Courtesy F. Dalzell.)

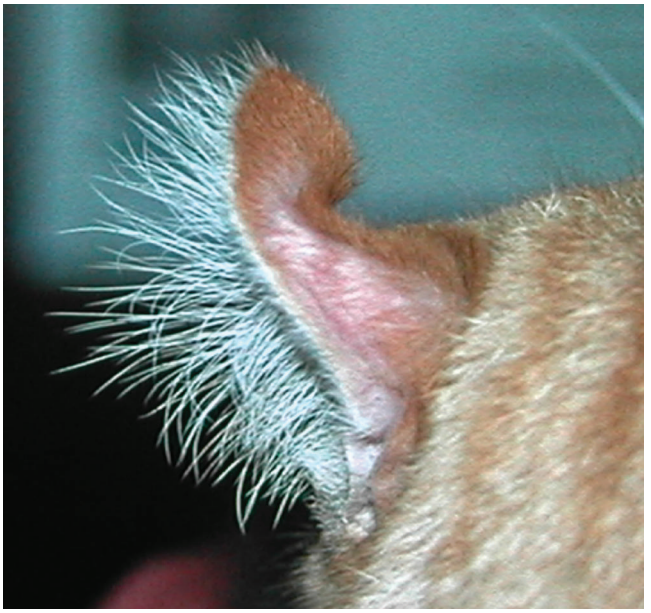

Figure 30-13. Polychondritis. Same cat as Figure 30-12. Close-up to show pinnal distortion. (Courtesy F. Dalzell.)

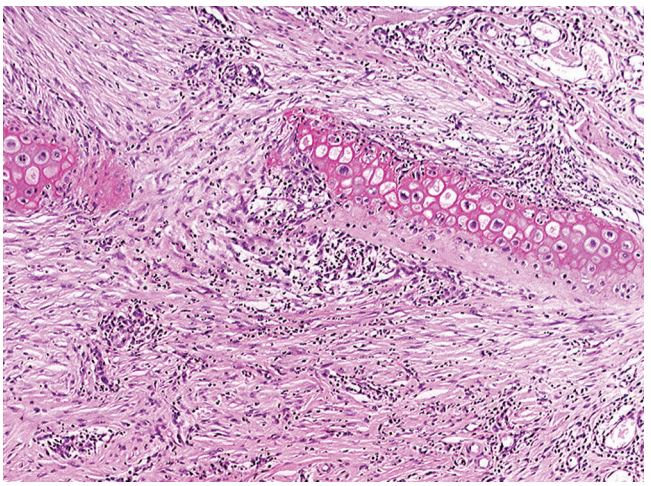

Figure 30-14. Subacute chondritis with neutrophilic infiltration of the deformed and hyperplastic cartilage. (H&E ×100.)

plastic cartilage with neutrophilic or lymphocytic chondritis, depending on the stage of the disease (Figure 30-14).

The similar disease in human beings also is rare (100 cases in 50 years) and affects cartilage in the ears and nose as a result of immune-mediated destruction of type II collagen.[25] The treatment of choice in human beings is glucocorticoids. Dapsone and indomethacin also have been used in nonresponsive cases.[25] Most human deaths are related to respiratory tract failure and cardiovascular complications resulting from cartilaginous collapse and vasculitis.[26,27] However, glucocorticoid therapy did not improve the clinical condition of one feline case significantly,[24] whereas disease in the other patient appeared to be self-limiting.[23] Recommending treatment protocols or evaluating their efficacy in cats is difficult when most cases of this rare condition are lost to follow-up.

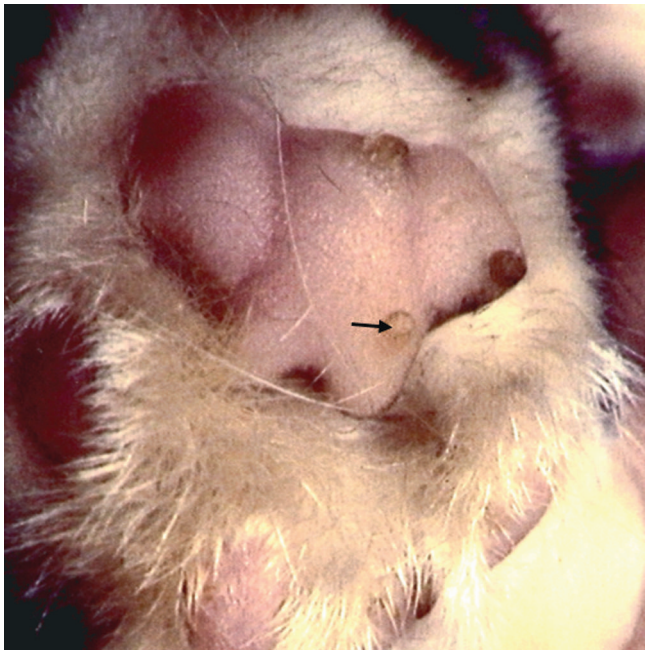

Figure 30-15. Feline focal acantholytic dyskeratosis of the footpads. Horny lesions *(arrow)* ulcerate to leave circular, dark-colored pits. (Courtesy M.H. Heimann.)

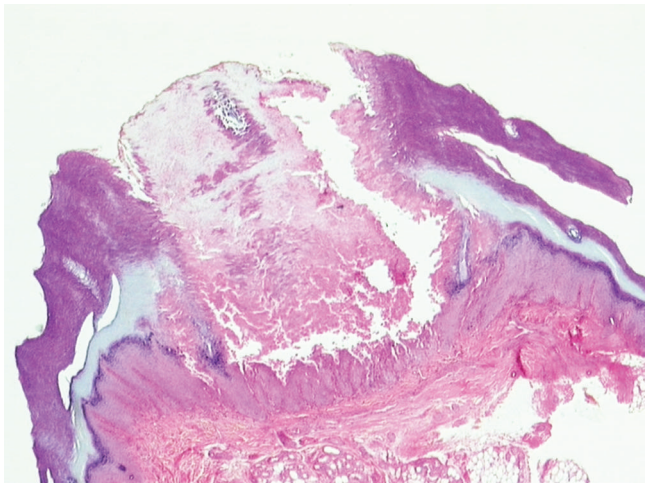

Figure 30-16. Feline focal acantholytic dyskeratosis of the footpads. Low-power histological view of acantholytic area with column of hyperkeratosis/parakeratosis. (H&E ×40.) (Courtesy M.H. Heimann.)

Feline Focal Acantholytic Dyskeratosis of the Footpads

This condition has been described in an 8-year-old cat that had nonregressing verrucous to cutaneous hornlike lesions of all footpads with erosions and formation of pits[28] (Figure 30-15). Histologically, the lesion was characterized by foci of acantholysis and dyskeratosis with vertical columns of parakeratosis (Figure 30-16). Clefts were at the spinous layer of the epidermis and contained "corps rond" (rounded epithelial cells with dark eosinophilic cytoplasm and condensed or pyknotic nuclei) and rafts of cells (Figure 30-17). The surrounding nonacantholytic cells had dense, irregular, and more numerous

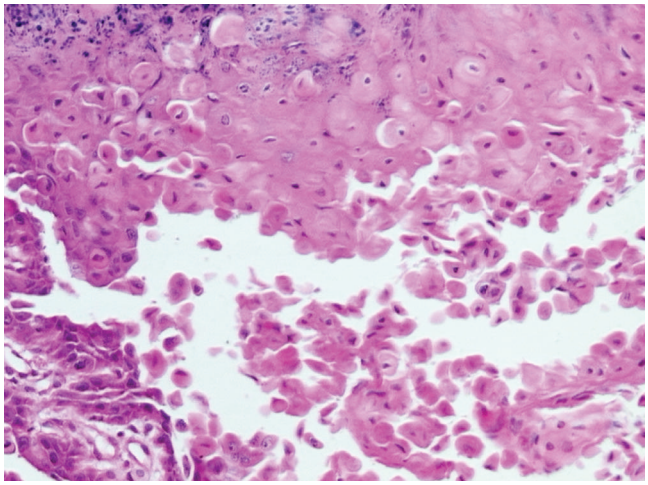

Figure 30-17. Feline focal acantholytic dyskeratosis of the footpads. High-power photograph of acantholytic cells of the spinous layer and large keratohyaline granules in the granular layer above. (H&E × 400.) (Courtesy M.H. Heimann.)

keratohyaline granules as seen in viral verrucous lesions. Mild inflammation, present only where lesions extended to the basal layer, was superficial. Immunochemistry for IgG revealed intercellular deposition, and transmission electron microscopy showed intercellular deposition of homogenous, dense material.

Immunochemistry for papillomavirus was negative and the cat was consistently feline leukemia virus (FeLV) negative, so the condition was not FeLV cutaneous horn (see Chapter 2). The histological appearance was similar to Darier's disease (keratosis follicularis) in human beings. However, Darier's disease is a follicular genodermatosis worsening in summer. The condition in this cat was not follicular and was nonseasonal for 6 years. No related cats were affected. "Focal acantholytic dyskeratosis" also is a histological feature of other conditions in human beings, including some types of pemphigus. The condition may be an unusual form of pemphigus foliaceus (see Chapter 29).

INFECTIONS

Mycetomas

Persian Cat Pseudomycetoma (Dermatophytic Granuloma)

This lesion is the exception to the rule that dermatophytes are not invasive and only attack keratin. *Microsporum canis* is the most common cause of the dermal nodules, which usually start on the back at the base of the tail (Figure 30-18). Ulceration is common, and the disease usually is relentlessly progressive. It was first described in 1975[29] with several cases recorded in North America during the next decade.[30-32] The combination of breed and histopathology (Figure 30-19) is diagnostic but may be confirmed by culture. The immune system of the Persian cat and whether the breed can mount curative T-cell responses probably are implicated in the pathogenesis, because no special features have been attributed to the isolated dermatophytes. Persian cats suffer from this disease and idiopathic facial

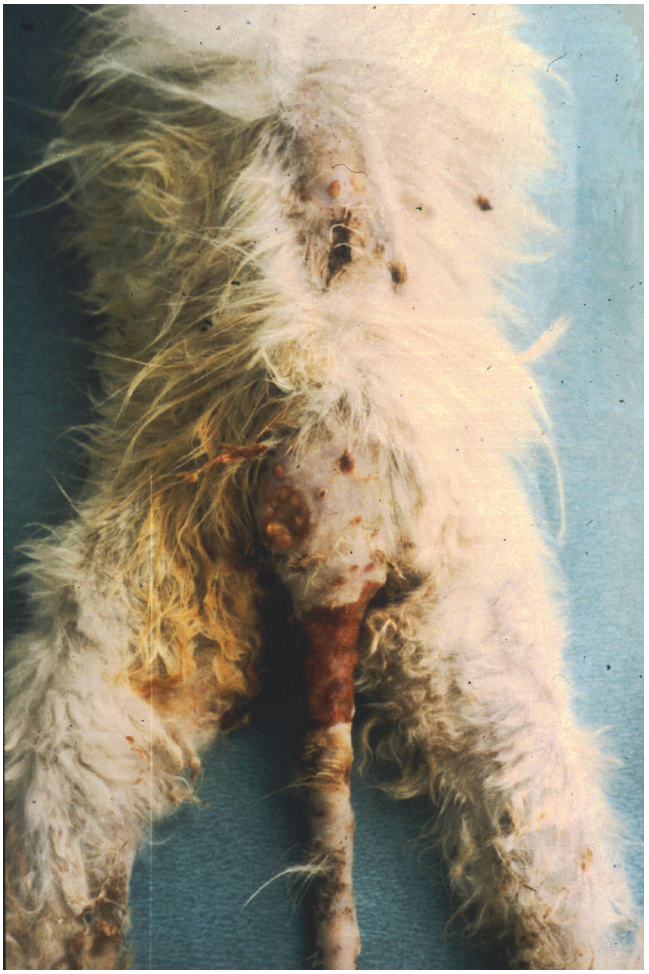

Figure 30-18. Dermatophytic mycetoma. Persian cat with dorsal tail-base, ulcerating nodules.

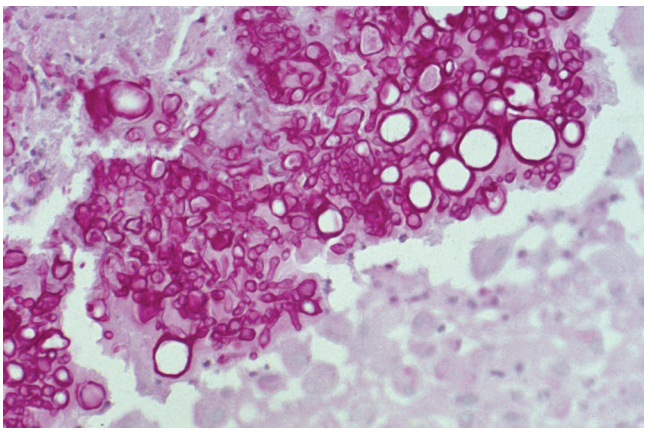

Figure 30-19. Dermatophytic mycetoma. Histopathology showing yeast-like budding hyphae within necrotic debris. (PAS ×400.)

dermatitis, which suggests that the breed has unusual genetic traits associated with aberrant immune reactions.

Fungal Mycetomas Including Cryptococcosis

My experience in the temperate United Kingdom has been that all of these mycetomas are rare. *Cryptococcus* is classified as a systemic mycosis with variation in strain virulence. It used to be described in association with immunosuppression, particularly with FIV and FeLV. However, systemic disease or immunosuppression is not always present.[33] In temperate regions, it appears to be an increasingly rare, opportunistic, subcutaneous infection, similar to other fungal mycetomas. The classic lesions are facial/nasal nodules, indistinguishable clinically from lesions caused by other saprophytic fungi of intermediate virulence.[34] The yeast form of the fungus (seen in skin lesions) does not produce aerosols and is not infective.

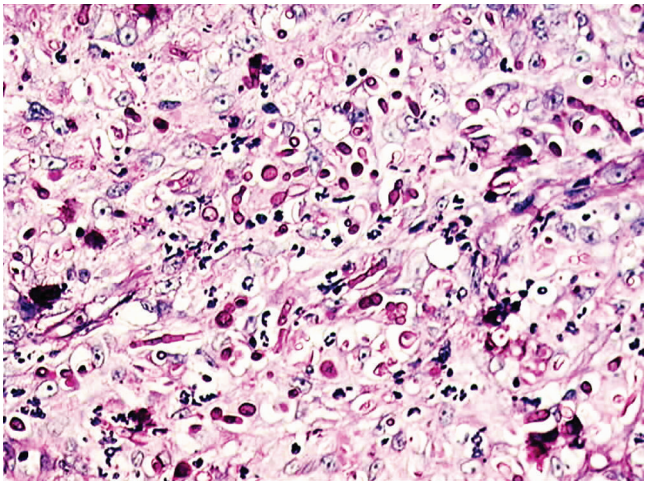

Figure 30-20. Mycetoma. Histopathology of a subcutaneous fungal mycetoma from the ear of a cat showing yeast and budding hyphal forms. (PAS ×400.)

In the temperate United Kingdom, most mycetomas occur in cats from the warmest (southeast) area of England and are on the legs and feet. A few appear on the nose and tail. Cats that dig in ground contaminated with pigeon droppings are affected most commonly. The lesions are well circumscribed and usually are removed surgically and submitted for histopathology as neoplasms (Figure 30-20). None of the cats I have seen with foot or leg infections have been immunosuppressed, FIV-positive, or FeLV-positive. Because cats tend to dig in the same places, they may become reinfected at a later date, which produces another mass requiring excision.

Bacterial Disease

Mycobacterial Granulomas

"Leprosy" was not uncommon in the 1970s, with a worldwide distribution. As many as 44 cases could be found for review in western Canada.[35] The disease was most prevalent near coasts, so rats from ships were suggested as one source of infection. It was easy to diagnose because the organisms are plentiful in the granulomas despite being difficult to culture (Figures 30-21 and 30-22). Some cases from New Zealand were proved to be due to *Mycobacterium lepraemurium* (rat leprosy), but *M. avium* has been reported subsequently as a cause of "leprosy-like" lesions in cats.[36,37]

The last 20 years have seen a decrease in the prevalence of "leprosy," possibly because of changes in opportunities for contact between feline and rodent reservoir hosts. *M. avium* infection may now be the main cause of disease in some

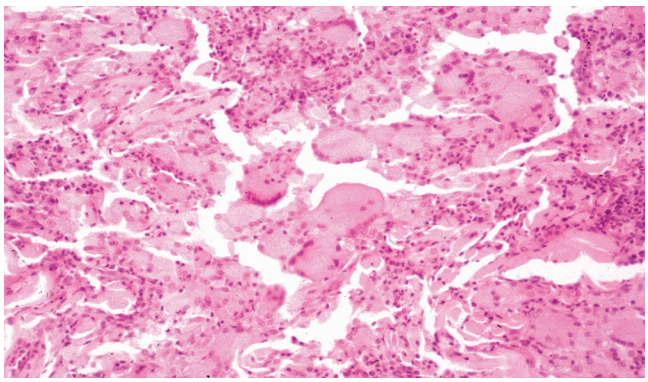

Figure 30-21. Leprosy. Granuloma showing many giant cells. (H&E ×400.)

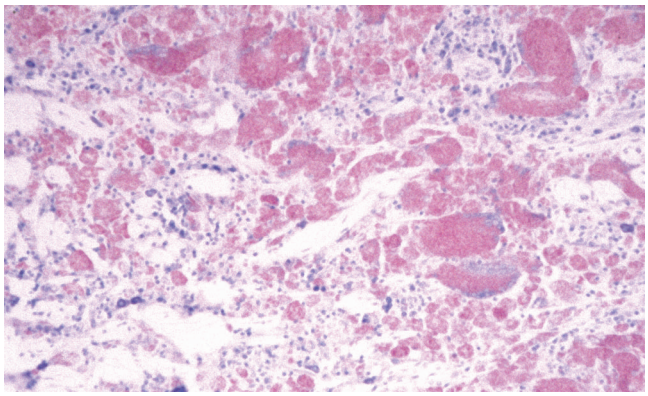

Figure 30-22. Leprosy. Granuloma with numerous acid-alcohol–fast organisms. (Ziehl-Neelsen ×100.)

Figure 30-23. Feline sarcoid. Typical clinical appearance: a small nodule close to the nasal philtrum. (Courtesy J.P. Teifke. Copyright Veterinary Dermatology, Blackwell Publishing.)

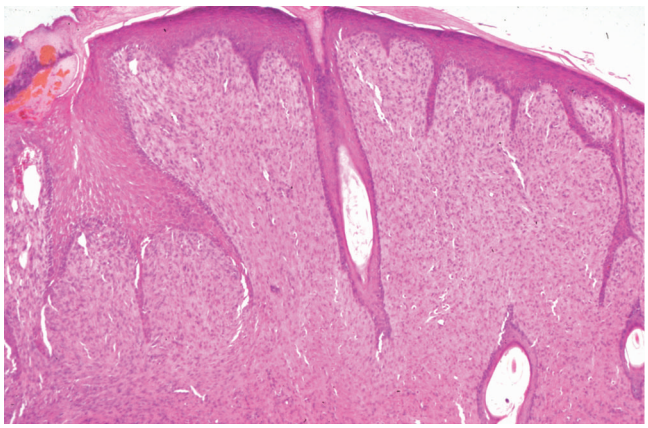

Figure 30-24. Feline sarcoid. Typical histopathology showing resemblance to an equine sarcoid. Note irregular epidermal hyperplasia and fibroblastic proliferation. (Courtesy J.P. Teifke. Copyright Veterinary Dermatology, Blackwell Publishing.)

locations, with birds a significant reservoir of mycobacterial infection transmissible to cats.

Feline tuberculosis, caused by *M. microti* (which also may be a rodent form because it is most common in hunting cats) also has been recognized in the last decade.[38] Whether this is a new disease or simply recent recognition of an existing syndrome is uncertain. The most common findings are cutaneous nodules and/or submandibular lymphadenopathy, but intestinal lesions also may occur. The skin lesions are pyogranulomatous without giant cells and contain rare organisms. Lymph nodes are granulomatous with necrosis as a constant feature.

Intradermal and serological tests are unreliable for diagnosis, and culture of organisms takes 6 weeks. The zoonotic potential of infected oral fluids and feces is uncertain, but to date, no record exists of infection of human beings from cats. In common with "leprosy," this mycobacterial infection usually remains localized to skin and lymph nodes, so surgery is the treatment of choice for both diseases. Enrofloxacin combinations given for approximately 5 months also have resulted in clinical remission.

Differential diagnoses include granulomas and pyogranulomas resulting from a wide variety of saprophytic, opportunistic, and fast-growing mycobacterial species (including *M. smegmatis, M. phlei,* and *M. fortuitum-chelonae*) and *Rhodococcus equi*.[39-42]

Viral Infections

Feline Sarcoid

Solitary skin fibropapilloma is a rare condition reported in young cats in North America, Australia, and Europe. Yager and Wilcock[43] reported 14 cases in dogs and cats in 13,000 biopsies over 3 years. The first cases in the United Kingdom and Sweden were published by my practice in 1998.[44] Lesions often are on the upper lip (Figure 30-23), but the lesions also may be on the hind legs. The associated lymph node sometimes is swollen. The incidence in my laboratory is approximately 5 per 20,000 submitted biopsies.

Yager and Wilcock suggested the lesions were not recurrent; however, local recurrence has been reported subsequently.[45] The main differential diagnosis is fibrosarcoma. However, the slow growth and histological features of epidermal hyperplasia and mild cytological abnormalities of the fibrous tissue are not typical of fibrosarcoma in young cats (Figure 30-24).

PCR investigations have shown that the disease is due to a strain of bovine papillomavirus.[46,47] The virus is present in the connective tissue and not the epidermis. Because the pathogenesis and pathology are similar to equine sarcoids, the term

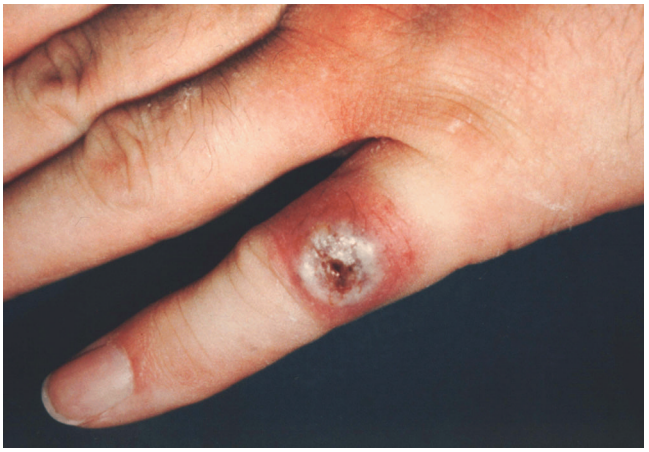

Figure 30-25. Orthopox infection. Human orthopox infection after handling an infected cat. The well-demarcated ulcer is surrounded by necrosis of the epithelium and a zone of erythema. (Courtesy Ashley Wilson.)

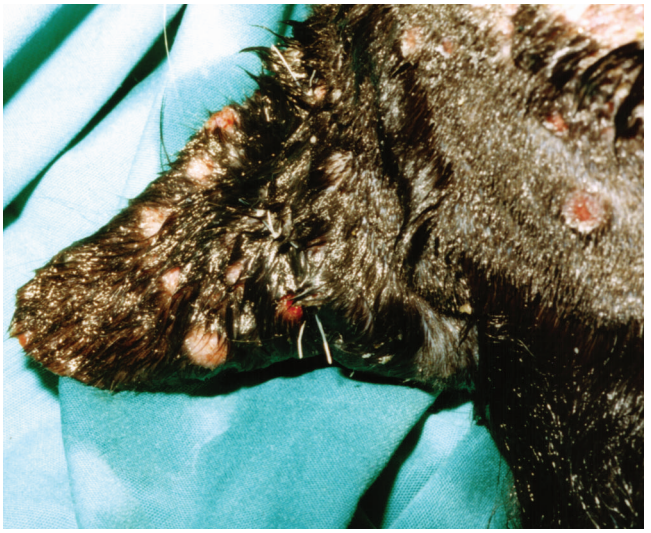

Figure 30-26. Orthopox infection. Multiple, well-demarcated, ulcerated, and inflamed lesion on the pinna and head of a cat. The spread of lesions suggests this is the viremic stage, approximately 1 week after the primary lesion. Removal of scabs may result in bleeding. (Courtesy S. van Poucke.)

feline sarcoid has been suggested rather than fibropapilloma (see Chapter 2).

Reports exist of other rare papillomavirus-associated skin lesions in cats.[48,49] One report of multicentric squamous cell carcinoma suggested a viral etiology for these lesions,[50] although viral etiology was not suggested in another report of 12 cases.[51] None of these proliferative lesions likely are associated directly with FIV or FeLV infection, although as in human beings, immunodeficiency may allow papillomavirus infections to flourish.

Orthopox Infection (Cowpox or Catpox)

This infection is widespread in Europe and Asia, although no cases have yet been reported from the Americas, Africa, or Australia. The reservoir hosts of the virus are rodents, particularly the bank vole (*Clethrionomys glariolus*), field vole (*Microtus agrestis*), and wood mouse (*Apodemus sylvaticus*).[52] Other hosts include cattle and foxes, and antibodies have been detected in rats. It is therefore a disease that, with its lack of species specificity and viral strain variation, could spread to other areas.

The European Union has funded major studies of the epidemiology of this infection because it is an excellent model for zoonotic diseases. The reservoir host species in the United Kingdom have peak populations in late summer and autumn, so the disease is transmitted accidentally to other animals at this time. The years in which the disease is diagnosed most frequently are those with the highest rodent populations.

In endemic areas, this is an important disease to recognize and differentiate from other diseases. Systemic disease may be induced if steroids are administered, and this disease is a zoonotic infection with cutaneous, ocular, and systemic disease (even death) recorded in human beings (Figure 30-25). Transmission to dogs and zoo animals also is possible.

The presentation is variable,[53] but ulceration is invariable. The disease has a primary lesion, often on the head or feet at about 6 days postinfection, then viremia occurs with widespread skin lesions approximately a week after the primary lesion (Figures 30-26 and 30-27). The lesions are not pruritic and have sharply defined borders. Clinically, they may be

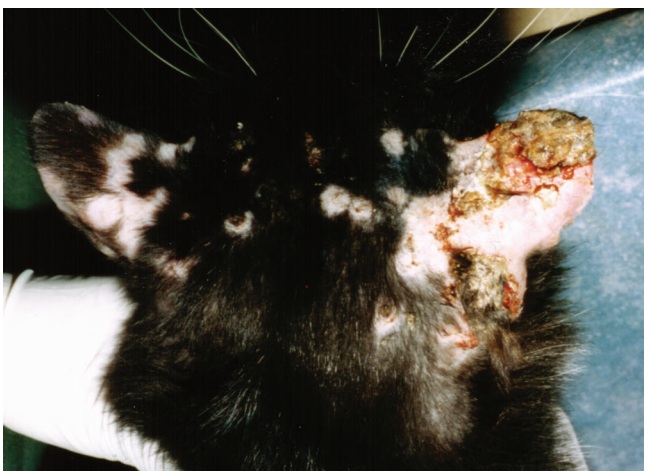

Figure 30-27. Orthopox infection. Crusting and alopecia associated with older lesions. Same cat as Figure 30-24, 2 weeks later. The lesions remain well demarcated. (Courtesy S. van Poucke.)

mistaken for hypersensitivity (eosinophilic ulcers) and parasite infestations and pemphigus or squamous cell carcinoma of the digit. Recovery takes several weeks, but the disease may be fatal in kittens and immunosuppressed cats (including iatrogenic steroid-induced immunosuppression). No specific treatment exists.

The histopathology usually is diagnostic in early lesions with characteristic inclusion bodies. However, even in their absence, histological necrotizing folliculitis in late summer or autumn should be considered diagnostic until disproved in endemic areas (Figures 30-28 and 30-29).

Other Viral Infections

With newer techniques such as immunohistochemistry and electron microscopy, identification of infections has become easier with viruses such as FeLV, herpesvirus-1, and papillomavirus demonstrated in cases of dermatitis.[54]

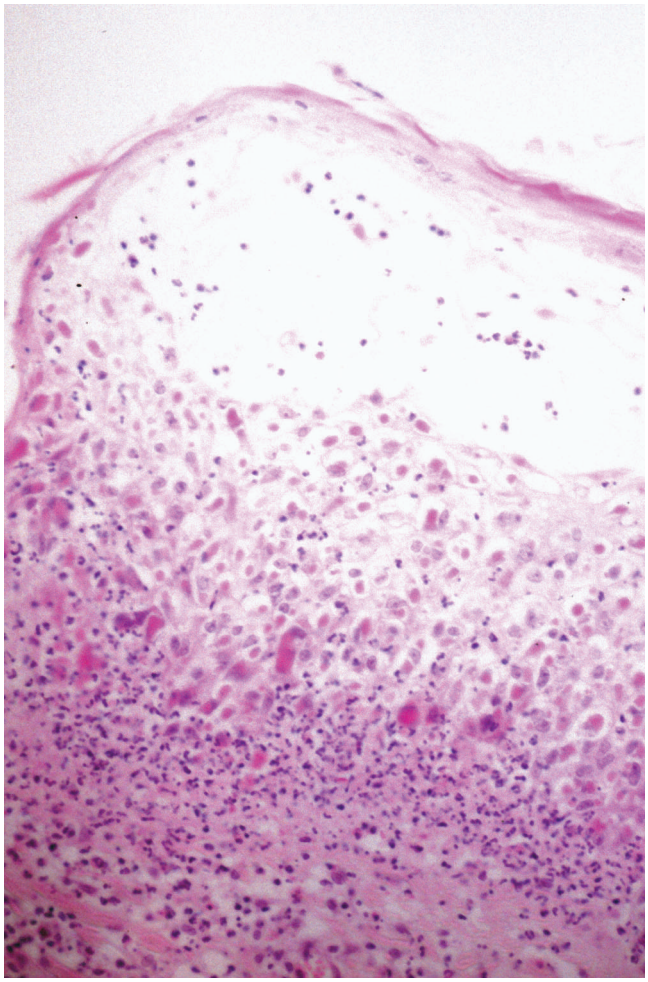

Figure 30-28. Orthopox infection. Photomicrograph showing a fragile primary vesicle. This is necrosing. Pink, variable-sized and variable-shaped inclusion bodies are visible near the base of the vesicle. (H&E ×100.)

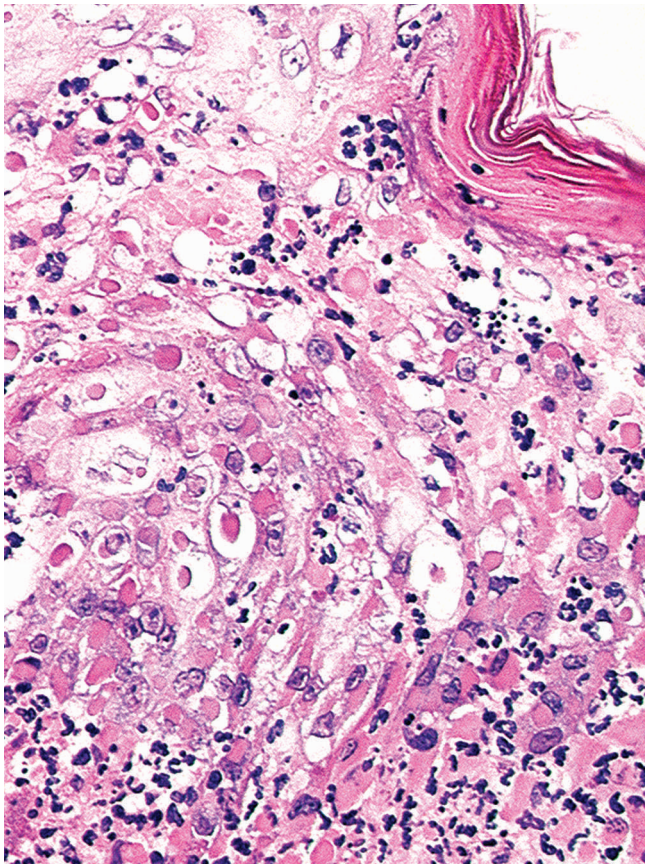

Figure 30-29. Orthopox infection. Photomicrograph with keratinized surface of the skin at the top right. Both surface and follicular epithelium are undergoing necrosis with multiple pink, variable-sized, and variable-shaped inclusion bodies. Most nuclei, including those of infiltrating neutrophils, are pyknotic or undergoing karyorrhexis. (H&E ×400.)

Herpesvirus-1 may cause ulcerative, crusting dermatitis of the nasal planum and haired skin of the face (Figure 30-30).[55] Microscopically, necrosis and ulceration occur with intranuclear inclusion bodies in the epithelium of the surface and follicular epithelium. The disease is clinically and pathologically similar to that caused by orthopox virus. Both infections occur in exotic cats,[53,56] and stomatitis and conjunctivitis are possible clinical signs of both diseases. Microscopic differentiating features are the type of inclusion body (eosinophilic in pox viral infections and basophilic in herpesvirus). The inflammation is predominantly eosinophilic in herpesvirus infection but not in pox virus infection (see Chapter 2).

Systemic viruses such as FeLV and FIV induce immunodeficiency, so recurrent skin infections are common. In human beings, and probably in dogs, some syndromes previously ascribed to drug reactions are emerging as viral diseases.[57] The same probably is true in cats because no provocation testing for drugs is done.[58] Epithelial syncytial formation (Figure 30-31) is a feature of a number of viral diseases and has been recorded in relation to FeLV infection.[54,59]

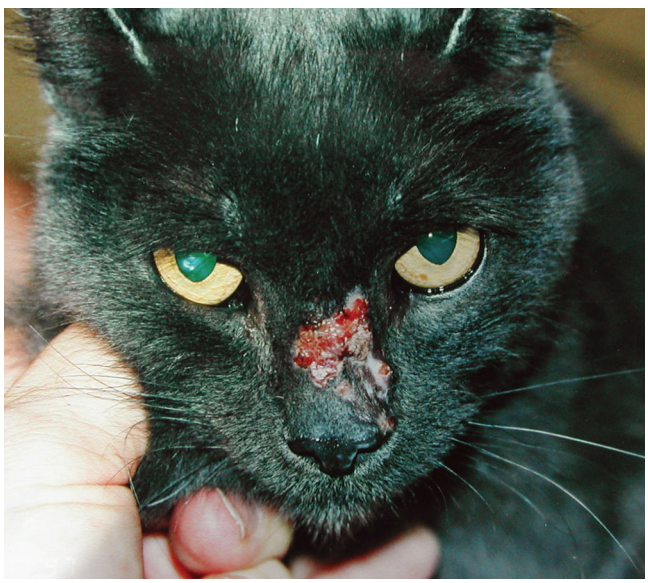

Figure 30-30. Herpesviral infection. Ulcerative dermatitis of the face of an infected cat. The lesion healed almost spontaneously after persisting for at least 7 months and then recrudesced at the same site for unknown reasons. The recurrent lesion is depicted in the photograph. (Courtesy A.M. Hargis. Copyright Veterinary Dermatology, Blackwell Publishing.)

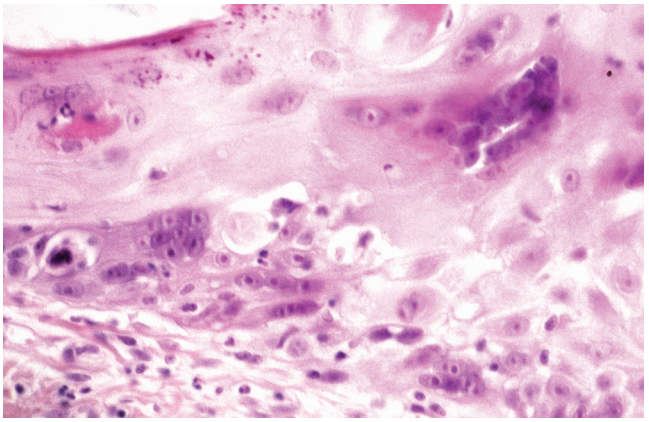

Figure 30-31. Syncytia formation and dyskeratosis in epithelium of a cat. (H&E ×400.)

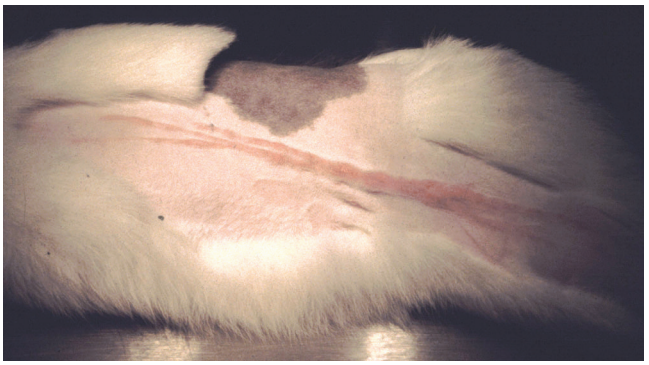

Figure 30-32. Linear granuloma. The lesion measured 43.5 cm in length. (Courtesy Jeremy Hopkins.)

Hypersensitivity

Hypersensitivity is the most common feline dermatopathological diagnosis with a bewildering variety of patterns, including self-induced alopecia; eosinophilic/miliary dermatitis; granulomas; pruritus of the head, neck, and pinnae; and chronic neck ulceration. At the tissue level, the complex reactions involve Langerhans cells, T-helper cells, mast cells, and eosinophils. Mast cells are prominent in most feline hypersensitivity reactions, often migrating into the epidermis. Specific types of mastocytosis also have been described.[60]

Traditionally, the disease is classified by its eosinophil content into granulomas, plaques, and ulcers. These have been shown to be a continuum.[61] We also recognize eosinophilic diseases, such as idiopathic facial dermatitis of Persian cats and herpesvirus-1 infection, which are not primary hypersensitivities.[62] A major reclassification may be needed (see Chapter 26).

Linear Granuloma

Linear granulomas may be truly linear and are found frequently on the caudal thighs, face, and oral cavity. The longest lesion in the author's case material was 43.5 cm long (Figure 30-32). It has been suggested that the linear configuration of lesions is because they follow meridia used in acupuncture. Some are eosinophilic and some are not, but "collagen degeneration" has been shown to be due to eosinophil degranulation.[63] Anecdotal evidence shows that granulomas without eosinophils respond

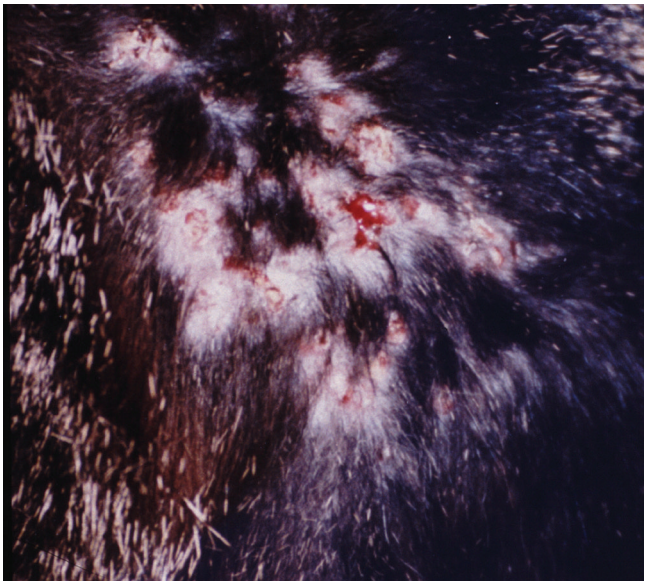

Figure 30-33. Perforating dermatitis. Bleeding exophytic lesions on the shoulder of a cat.

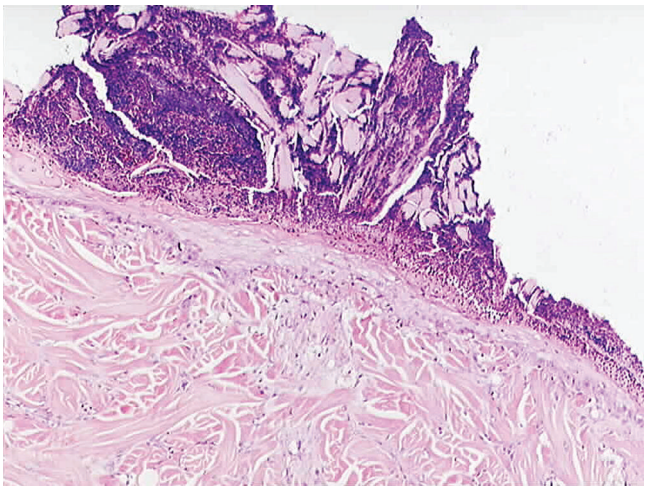

Figure 30-34. Perforating dermatitis. Photomicrograph of the exophytic collagen necrosis. (H&E ×40.)

to ascorbic acid, which stabilizes collagen and reduces free radical damage. The same treatment is helpful in perforating dermatitis[64] (Figures 30-33 and 30-34). This also is an eosinophilic disease, and the two could be related.[62] The precise pathology depends on how close to the surface the lesion is formed.

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Chapter 31

Drug Therapy in Cats: Precautions and Guidelines

Mark G. Papich

THE PROBLEM WITH DRUG FORMULATIONS IN CATS

Palatability, ease of administration, and dispensing factors are among the considerations in drug formulation for cats. Most animal drugs are designed for dogs, but little consideration is given to the needs of cats. Subsequently, we often rely on administration of human or canine dosage formulations for cats. If we are lucky, a scored tablet is available that can be adjusted for a cat-sized dose, or a pediatric human formulation may exist. Too often, however, we simply have to crush a tablet or prepare a compounded formulation to improve the ease of administration to cats.

Veterinarians sometimes assume that drugs intended for dogs or people share similar pharmacokinetics in cats. This is often not true. Cats have a simple digestive tract that is shorter than in dogs or human beings. Cats compensate with a slower intestinal transit time, and higher permeability of drugs and other compounds than dogs or human beings.[1] Cats have smaller stomachs than dogs because their eating patterns are associated with smaller, more frequent meals. These differences in anatomy may account for differences in absorption between cats and other species.

The gastric emptying time and intestinal transit of medications are affected by feeding; food tends to have a significant slowing effect in cats.[2,3] Drugs that require dissolution because of poor solubility have a faster transit time and poor oral absorption when administered to an unfed cat, compared with giving the medication with food. This was shown for chloramphenicol palmitate, for example.[4] This also is a possible explanation for their problem with effectiveness from oral prednisone (to be discussed below). Because cats resist frequent dosing, slow-release or sustained-release medications are desirable, but few are available. One of the problems with currently available slow-release medications is that they are designed for use in people. Because of the aforementioned differences in the gastrointestinal tract between cats and human beings, slow-release drugs may be released poorly after oral administration to cats unless they are accompanied with food. However, the release of human extended-release or controlled-release medications also depends on the matrix of the tablet, its coating, and the drug's solubility.

Palatability also is a large problem. Tablets that must be crushed or broken to deliver a smaller dose size to cats may be too unpalatable for oral use. Several antibiotics are examples of this problem; cats react frequently to oral administration of metronidazole, clindamycin, or trimethoprim-sulfadiazine with salivation and refusal to accept the medication.

When drugs are administered to cats, either a portion of a tablet must be given, or the drug must be reformulated into a capsule. Because ill cats usually are anorectic, and cats in general do not drink water frequently, solid-dose forms can become trapped in the esophagus of cats (see Chapter 10). In two studies, oral administration of capsules to cats resulted in problems. When capsules containing barium sulfate were followed radiographically, they became entrapped in the midcervical region of the esophagus 53 per cent of the time.[5] The capsules passed when followed with food. In another study, a dry capsule given to cats was retained in the esophagus for greater than 300 seconds 63 per cent of the time. Wet capsules passed 97 per cent of the time at 30 seconds and 100 per cent of the time thereafter.[6] The location of the entrapment of capsules is particularly disturbing because some medications given to cats, such as doxycycline, tetracycline, propranolol, iron supplements, and bromide, were shown to cause esophageal lesions in experimental cats.[7,8] Doxycycline has been associated with esophageal stricture in cats.[9]

TRANSDERMAL DRUGS

The administration of transdermal drugs to animals was reviewed recently[10] (see Chapter 18). The success with some

transdermal drugs (antiparasitic agents and fentanyl) has stimulated considerable interest in formulation of a wide range of other drugs for this route. Compounding veterinary pharmacists have advertised the ability to formulate transdermal medications from existing forms of antibiotics, cardiovascular drugs, antithyroid drugs, analgesics, corticosteroids, and antidepressants. Drugs have been combined with penetration enhancers to facilitate transdermal absorption. One popular example of a penetration enhancer is pluronic lecithin organogel (PLO), which is lecithin (derived from eggs or soybeans) mixed with isopropyl palmitate and a poloxamer (Pluronic). The ingredients in PLO act as surfactants, emulsifiers, and solubilizing agents. Although the use of PLO is popular among the veterinary compounding pharmacies, no successful commercial formulations have combined PLO with systemic drugs. Usually, animal owners are instructed to apply the drug to the inside of the animal's ear because this location cannot be licked with the tongue and it usually is not covered with hair.

At the time of this writing, most published reports of transdermal application of drugs to cats showed that absorption was incomplete, nonexistent, or highly inconsistent among cats. Yet some pharmacies advertise their willingness to provide these formulations to veterinarians via the Internet and by promotion at national trade shows. Drugs examined so far have included glipizide, dexamethasone, buspirone, amitriptyline, fentanyl, methimazole, morphine, fluoxetine, and diltiazem.[11-19] Glipizide was absorbed poorly in cats, with bioavailability equaling only 4 to 30 per cent of that observed from the oral formulation.[16] Fluoxetine transdermal bioavailability was only 10 per cent of that compared with oral absorption of an approved human formulation. However, if a large dose was administered (10 times the oral dose), plasma concentrations equal to that achieved after oral administration were achieved,[15] although repeated topical application caused dermatitis. Although methimazole was shown to be poorly absorbed in a pharmacokinetic investigation,[14,17] a clinical investigation provided evidence of efficacy with repeated transdermal applications.[13] When dexamethasone was administered topically in PLO, absorption in cats was negligible.[18] Systemic absorption from topically applied amitriptyline or buspirone in a PLO vehicle was poor and should not be considered a reliable route for treatment.[19]

The most common concern associated with these formulations is a lack of efficacy because of poor absorption or decreased drug stability. However, an increased risk of toxicity also is a potential problem. If the drug ordinarily is poorly bioavailable after oral administration because of a large first-pass effect, higher systemic levels after transdermal application may result. Obviously, if the drug is toxic to human beings, the animal owner who applies the medication also is at risk. If the cat's skin becomes inflamed from a dermatological problem or irritation caused by the drug or excipient, this also may affect drug absorption.

EXTRAPOLATING DOSES FROM OTHER ANIMALS TO CATS

When information on drug dosing is not available from a drug sponsor, extrapolation from human beings or other animal species is necessary. Obviously, when doses are derived under these circumstances, much is left to chance with a risk of error and adverse reactions.

When drug doses for a specific species are not known, doses are extrapolated with use of the principles of allometric scaling; drug doses are adjusted according to body size. The principles of allometric scaling can be used to adjust a dose when body size can be related to certain pharmacokinetic parameters, such as clearance and half-life.[20] These can be scaled allometrically when the pharmacokinetic parameters are related to a physiological function such as metabolism or renal clearance. These relationships usually are exponential rather than linear. For example, if *Y* is the physiological parameter (e.g., clearance), the relationship to body size is

$$Y = a(BW)^b$$

where *a* is a coefficient, *BW* is body weight, and *b* is the allometric exponent.[21] In principle, dosing allometrically to veterinary species appears rational, but allometric relationships do not apply to the majority of drugs. The traditional method used to apply allometric scaling has been to use an estimate of basal metabolic rate (BMR) to derive the exponent (*b* in the equation above) used to calculate the pharmacokinetic parameter. However, problems arise in application of this principle to cats, because the allometric exponent for cats is smaller than for dogs of similar size.[22] Cats less than 2.5 kg body weight (kittens) have an allometric exponent of 0.67, similar to dogs. But adult cats have a much lower exponent of 0.4. Overestimating the value of the exponent may cause an overdose in adult cats using allometric formulae derived for other animal species. This raises a doubt about the accuracy of cross-species extrapolation of drug doses for cats based on allometric calculations.

Even when drugs have been scaled allometrically, the ones best predicted are those that are cleared predominantly by the kidneys and exhibit low protein binding. Some antibiotics, such as fluoroquinolones or aminoglycosides, may be examples of this case. For other drugs, many factors can cause differences in clearance, such as rates of biotransformation and genetic polymorphisms.[21] Several decades ago, Brodie characterized the ability to predict metabolism of drugs between people and animals as "pure luck" because of the wide differences in drug metabolizing enzymes.[23] In a detailed review, Lin concluded that, "unlike anatomical and physiological parameters, there is no distinct allometric relationship between the biochemical parameters (protein binding and enzyme activity) and body weight."[24] Therefore some medications can be scaled to the cat's body size based on allometric scaling. However, to assume without supporting evidence that this principle applies to all drugs is risky.

CATS VERSUS OTHER SPECIES

Dogs are used often for preclinical studies performed by drug manufacturers, but fewer drug studies are done using cats. Most approved small animal drugs are for dogs, but safe and effective drugs are needed for cats as much as any other species. Without specific pharmacokinetic studies performed, extrapolation from dogs or human beings to cats is risky. The classical example of impaired drug clearance for cats is that of acetaminophen (Tylenol) or salicylate (aspirin). Cats do not tolerate these drugs well and can be overdosed easily.[25,26] Acetaminophen exhibits nonlinear clearance in cats. Therefore the higher the dose, the slower the rate of excretion. Evidence exists that other drugs also show impaired clearance in cats and

are prone to cause toxicity if they are given at the same rate (on mg/kg basis) as for dogs. Among these drugs are lidocaine, chloramphenicol, digoxin, carprofen, azathioprine, and the opiates. Unique toxicities also are possible, such as the susceptibility of cats to cisplatin toxicosis, the idiosyncratic hepatic injury from diazepam, and bronchitis from the anticonvulsant potassium bromide.

Despite these cited examples, an incorrect assumption is that doses for all other drugs should be lower for cats compared with dogs, or that they should have problems with all antiinflammatory medications. Many drugs, including some nonsteroidal antiinflammatory drugs (NSAIDs) can be used safely. The following discussion focuses on some of the more commonly used systemic drugs in veterinary dermatology.

CORTICOSTEROIDS

Dose recommendations published for corticosteroids and cited in other chapters of this section state that cats may need higher doses than dogs and that cats are more resistant to the side effects than dogs.[27] Why? The reasons for this are unknown, but pharmacokinetic explanations may include differences in the rate of metabolism of corticosteroids in cats compared with dogs, a difference in extent of oral absorption, or a difference in the population of receptors. Difficulty in administering oral medications to cats also may affect the perceived drug efficacy.

In the study by van den Broek and Stafford,[28] they showed that cats have approximately half the number of receptors in skin and liver for corticosteroids and the receptors have lower affinity. They proposed that this may account for the observed differences in corticosteroid resistance in cats compared with dogs.

Because prednisone must be converted metabolically to the active prednisolone, cats may be deficient in this capacity compared with other species. Horses also have been shown to have a deficiency in the ability to convert prednisone to prednisolone. The preliminary results available at this time indicate that cats either do not absorb prednisone orally as well as prednisolone or are deficient in the ability to convert prednisone to the active metabolite prednisolone once absorption is complete.[29] Relative bioavailability of prednisolone from administration of the pro-drug prednisone was only 21 per cent. This observation is consistent with the frequently cited recommendation in textbooks and review papers that cats are relatively refractory to oral administration of prednisone but respond when switched to another corticosteroid (for example, prednisolone, methylprednisolone, or triamcinolone) or an injectable form (e.g., methylprednisolone acetate, or DepoMedrol). In a study that examined 57 cases of pemphigus foliaceus in cats, triamcinolone was more successful at inducing remission than prednisone, or prednisone in combination with chlorambucil.[30]

ANTIHISTAMINES

Antihistamines block the histamine type-1 receptor (H_1) and suppress inflammatory reactions caused by histamine. The H_1-blockers have been used to control pruritus and skin inflammation in dogs and cats. However, as summarized by DeBoer and Griffin,[31] success rates in dogs have not been high. In spite of the lack of positive evidence to support their use, these drugs are an option for mildly pruritic animals or for the short-term treatment of pruritus in patients who do not tolerate corticosteroids. The exact mechanism by which they act is not certain. Presumably, they block action of histamine on the H_1 receptor. However, because histamine may not be an important mediator of pruritus in all patients, these drugs also may exert their effects by inhibiting mast cell degranulation.[32] The side effect of sedation also may play a role by decreasing the animal's urge to itch.

Commonly used antihistamines include clemastine, chlorpheniramine, diphenhydramine, and hydroxyzine. Clemastine (Tavist), an ethanolamine antihistamine, was effective in dogs, with 30 per cent of the dogs treated responding,[33,34] and was reported to be effective in cats, with a 50 per cent success rate.[32] Chlorpheniramine, diphenhydramine, and hydroxyzine are other drugs of this class used in dogs, but only chlorpheniramine has been reported to reduce pruritus in cats, with a 73 per cent reported success rate.

Side effects of antihistamines are primarily sedation and some antimuscarinic effects, but these have not been reported frequently. However, in cats a paradoxical reaction may be more of a problem. The antihistamines chlorpheniramine and diphenhydramine have caused excitement and restlessness in cats more than in other species (unpublished anecdotal observations).

PHOSPHODIESTERASE INHIBITORS

Pentoxifylline and other methylxanthines are believed to exert their mechanism of action via inhibition of the phosphodiesterase enzyme; therefore they have been given the name "phosphodiesterase inhibitors" or PDE-inhibitors.[35] PDE-inhibitors, by increasing cyclic-AMP, or via other mechanisms, produce antiinflammatory effects. They may inhibit T-cells in inflammatory dermatoses, decrease the synthesis of cytokines such as TNF-α, IL-1, and IL-6, and inhibit eosinophils. In human beings, pentoxifylline is used to improve blood flow through narrowed arteries because of the rheological property, in which it allows red blood cells to change shape. This property has not been shown to have a benefit for treating inflammatory diseases. Whether the improvement in patients with ischemic dermatoses is caused by improved blood flow (rheological effect) or via the antiinflammatory mechanisms is unknown.

Pentoxifylline was first used in veterinary dermatology for familial canine dermatomyositis (FCD) and contact allergy. More recently, it has been put forth as a treatment for atopic dermatitis[35] and erythema multiforme (EM). Pentoxifylline is available in a 400-mg tablet. Some veterinarians simply use dosing regimens that allow the use of a full tablet for a large-size dog. When tablets are broken or crushed for cats (e.g., 100 mg per cat), the taste is unpleasant. Intravenous infusions of pentoxifylline reportedly have been used in cats in experimental laboratories,[36] but no reports exist of the use of this drug in cats in a clinical setting. A side effect of phosphodiesterase inhibitors in people, and possibly cats, is vomiting.

DRUGS THAT AFFECT THE IMMUNE SYSTEM

Nitrogen Mustards

Cyclophosphamide is one of the nitrogen mustards and is one of the most potent immunosuppressive drugs available. Cyclophosphamide undergoes extensive metabolism via

cytochrome-P450 (CYP450) oxidation followed by spontaneous conversion. However, despite the complicated metabolism, no evidence exists that cats are more sensitive to adverse effects from cyclophosphamide than other animals. Actually, differences in metabolism may exist, which account for cats being more resistant to the adverse effects. In dogs, sterile hemorrhagic cystitis is caused by the toxic effects of metabolites on the bladder epithelium (especially acrolein) concentrated and excreted in the urine. No reports exist of this problem occurring in cats; therefore, they may be more resistant to this effect than human beings and dogs. When used clinically, the dose for cats is a total dose of 6.25 to 12.5 mg q24h 4 days per week.

Chlorambucil (Leukeran), also a nitrogen mustard, sometimes is used as a substitute for cyclophosphamide or azathioprine for the management of immune-mediated diseases. It has a similar action as cyclophosphamide but is one of the slowest acting of the class of nitrogen mustards. Although little has been published on the clinical use of chlorambucil, it may be effective in cats for immune-mediated diseases such as pemphigus foliaceus. Direct comparisons to other immunosuppressive drugs have not been reported. In one report, cats with pemphigus and eosinophilic granuloma complex (EGC) responded favorably with few side effects.[37,38] The most commonly cited dose is 0.1 to 0.2 mg/kg PO q24h. After remission, this dose is administered q48h. It is available as 2-mg tablets. It may be given with oral prednisolone, alternating days of administration of each drug.

Azathioprine

As first-line therapy or as an alternative to nitrogen mustard alkylating agents for treatment of immune-mediated disease, thiopurines have been administered in dogs and people but avoided in cats. The most common drug in this class is azathioprine (Imuran). It is metabolized in the liver to the active metabolite 6-mercaptopurine (6-MP). In vitro studies indicate that some metabolism may occur at target cells responsible for immune effects. Azathioprine interferes with de novo synthesis of purine nucleotides, which are important for lymphocyte proliferation. 6-MP inhibits T-cell lymphocyte function and helper cell effects on antibody synthesis, with little direct effect on B-cells. In people, it has been suggested that azathioprine is more effective for IgG-mediated disease, whereas cyclophosphamide is more effective for IgM-mediated disease. This theory has not been tested in animals.

Some veterinarians have administered azathioprine to cats at a total dose of about 6.25 mg per cat (⅛ tablet) q48h. Success has been reported with 1 mg/kg q48h for pemphigus.[39] However, doses of 2.2 mg/kg q48h produced profound neutropenia in cats.[40] Some veterinarians have administered 1.1 mg/kg q24h or q48h, but other references have discouraged its use in cats because of the bone-marrow–suppressing effects.[37] Differences in metabolism may explain the susceptibility in cats (discussed below under metabolism). Because cats may be at a risk of bone marrow suppression from administration of azathioprine, its use is discouraged until more accurate and safe dose recommendations are available. Nevertheless, some veterinarians have reduced the dose considerably and administered doses as low as 0.3 mg/kg q24h or q48h, which warrants careful monitoring of complete blood counts during treatment.

The susceptibility of cats to azathioprine toxicity may be related to their deficiency in the enzyme thiopurine methyltransferase (TPMT).[41-43] After azathioprine is converted to 6-MP, it is metabolized further by three routes to other metabolites. One metabolic route is via TPMT, which is responsible primarily for conversion to nontoxic 6-MP nucleotides. In human beings, genetic polymorphism determines high or low levels of TPMT. People with low TPMT activity are more responsive to therapy but have a high incidence of toxicity (myelosuppression); people with high levels of TPMT activity have low incidence of toxicity but lower efficacy.[44] Most of the human population has high TPMT activity, but about 11 per cent have low levels and are more prone to toxicity. In people with low TPMT activity, doses must be lowered. A wide range of TPMT activity occurs in dogs, but whether this correlates to myelotoxicity has not been established.[45,46] Cats have low TPMT activity,[41-43] which may explain their susceptibility to toxicity.

Cyclosporine

Cyclosporine is a fat-soluble, cyclic polypeptide fungal product with potent immunosuppressive activity. It has been an important drug used in human beings, primarily to produce immunosuppression in organ transplant patients. This drug binds to a specific cellular receptor and inhibits calcineurin, which reduces the T cell receptor–activated signal transduction pathway. Particularly important are its effects to suppress interleukin-2 (IL-2) and other cytokines. Via its action to suppress IL-2, it blocks activation of T-lymphocytes. The action of cyclosporine is more specific for T-cells as compared with B-cells. In atopic asthma in cats, cyclosporine does not inhibit mast cell degranulation, but tissue exposure ex vivo inhibited release of 5-hydroxytryptamine.[47] One important advantage in comparison with other immunosuppressive drugs is that it does not cause significant myelosuppression or suppress nonspecific immunity. It does not share the same side effects as corticosteroids and therefore has been used to spare, or substitute for, corticosteroids in patients with inflammatory diseases.

In veterinary medicine, cyclosporine has suppressed immune-mediated reactions in transplant patients and patients treated for dermatitis, perianal fistulas, keratoconjunctivitis sicca, and immune-mediated anemia. The use of cyclosporine for treating atopic dermatitis in dogs is now well established.[35,48-54] However, the response for autoimmune skin disease in dogs has not been encouraging.[51,55]

In dogs, the registered dose for atopic dermatitis is 5 mg/kg per day, which may be decreased to 5 mg/kg every other day in some patients. Cyclosporine is available in human formulation capsules of 25 and 100 mg, 20 mg/ml oral solution, and 50 mg/ml injection. The veterinary brand (Atopica) is available as 10, 25, 50, and 100 mg. The current formulation of Atopica has smaller capsule sizes available, which may allow for more accurate dosing in cats. Generic preparations also are available, but their absorption and pharmacokinetics have not been reported for animals; if used, using the modified formulation is important. Comparisons at our pharmacy have not demonstrated that the generic formulations are significantly less expensive than brand name products.

The disposition of cyclosporine after oral administration of the Neoral formulation has been studied in cats. Systemic absorption in cats is rapid, with peak concentrations less than 1 hour, absorption of 25 to 29 per cent, and half-life of 8.2 (+/– 3.3) hours, which are parameters similar to dogs,[56] but the

pharmacokinetics are variable among cats. As in dogs, ketoconazole inhibits enzymes responsible for clearance of cyclosporine in cats. The reduction is not as great as for dogs, but co-administration of ketoconazole (10 mg/kg) increased the plasma concentrations of cyclosporine in cats by approximately twofold.[57]

The best-documented indication for cats has been the use for kidney transplantation. To manage organ rejection in recipient cats,[58] a dose of 3 mg/kg q12h was used to achieve trough blood concentrations of 300 to 500 ng/ml. At NCSU, we routinely administer 25 mg/cat for suppression of immunity for transplantation and modify as needed with monitoring.

Treatment of feline skin problems has been reported mostly as small pilot studies in conference abstracts and therefore has not been evaluated rigorously. In one pilot study, a dose of 5 mg/kg/day orally for 1 month was administered to 10 cats with allergic pruritus and eosinophilic dermatosis.[59] Cutaneous lesions improved and reduced in approximately half of the cats; however, overall no significant improvement occurred. For treatment of inflammatory disease in cats, including eosinophilia granuloma complex, additional evaluations have been performed. A good response to a dose of 25 mg/cat was seen in six cases of eosinophilic plaque and three cases of oral eosinophilic granuloma.[60] A preliminary report indicated that cyclosporine at a dose of 6 to 7 mg/kg/day was effective for treatment of facial dermatitis of the Persian cat, although two cases became refractory after 6 months.[61] Another preliminary report indicated that cyclosporine improved the lesions in two cats with feline urticaria pigmentosa treated with a dose of 7.5 mg/kg PO q24h.[62]

The most common adverse effects of cyclosporine are anorexia, vomiting, and refusal to eat if cyclosporine is mixed with the food. This is managed best by a decrease in dose and/or splitting of the dose. Toxoplasmosis has been reported in cats treated with cyclosporine, in addition to secondary infection and malignancy.[57,58,63,64] These effects presumably are due to immunosuppression.

Routine blood monitoring of cyclosporine is not necessary, especially if a patient is responding as expected. However, monitoring may be helpful to identify a situation in which owner compliance is poor or to identify patients with either poor or enhanced absorption. When blood monitoring is performed for cyclosporine, the commonly used fluorescence polarization immunoassay (FPIA) performed on a commercial TDx (Abbott Diagnostics, Abbott Park, Illinois) overestimates the true cyclosporine concentration by approximately twofold. (That is, TDx assay reporting 500 ng/ml corresponded to an actual value of 250 ng/ml.) Therefore, with use of a specific radioimmunoassay or HPLC, true concentrations are measured. However, with use of a TDx fluorescence polarization assay (monoclonal whole blood), the feline concentrations are multiplied by 0.5 to obtain the true concentration. If blood monitoring is performed, the traditional sampling time has been a trough sample (collected immediately before the next scheduled dose). As stated above, trough blood sample measurements have been used to monitor cats that have had renal transplants.[58] However, a more recent trend is to use a sample collected at 2 hours after oral dosing because this correlates more closely with the area-under-the-curve (AUC) and may be more predictive of clinical response.[65] In the study cited earlier, the 2-hour sample (C_2) was better correlated to the AUC than trough concentrations and therefore may be a better value for monitoring. If this is considered for cats, levels are approximately twice as high at 2 hours compared with the levels at 12 hours.[56]

ANTIFUNGAL DRUGS

Please see Chapter 32 for a more detailed discussion of the use of antifungal drugs.

Griseofulvin is effective for treatment of dermatophyte infections, but long-term therapy often is needed. One report showed that doses of 50 mg/kg/day for cats were as effective as itraconazole for treatment of dermatophytosis.[66]

Griseofulvin is available in 125-mg and 250-mg capsules; 125-mg, 250-mg, and 500-mg tablets; and an oral syrup that is 125 mg/ml. At least 4 weeks often are needed for successful therapy and some patients require 3 months (or more) of continuous therapy. As many as 4 months may be necessary to treat onychomycosis. Cats need to be treated until they are culture-negative repeatedly.

Although griseofulvin has acceptable efficacy, its use has diminished in recent years because of the risks of adverse effects, need for administration with food, and long duration of treatment that is sometimes needed. Many dermatologists prefer to administer an azole drug instead (discussed later).

Cats appear to be the species most susceptible to the adverse effects of griseofulvin.[67] The adverse effects may be dose related and veterinarians should warn owners of the potential for toxicosis.[68] Do not administer to pregnant cats because of the clear association between griseofulvin therapy and congenital malformations in kittens.[69] Anemia and leukopenia have been observed in cats from griseofulvin treatment, particularly in cats infected with feline immunodeficiency virus.[67] Whether this is caused by high doses or is an idiosyncratic (non–dose-related) reaction is not understood. These effects resolve in cats when treatment is stopped, but irreversible idiosyncratic pancytopenia has been reported. Other adverse effects that may be seen include anorexia, depression, vomiting, and diarrhea.

Imidazole Antifungal Drugs: Triazoles and Azoles

Ketoconazole, like other imidazoles, inhibits the conversion of lanosterol to ergosterol by the 14-demethylase system (a P-450 enzyme). By inhibiting ergosterol synthesis, ketoconazole damages cell wall membranes by making them more permeable. Ketoconazole has a wide spectrum of activity that includes yeast (e.g., *Malassezia pachydermatis)*, fungi, dermatophytes, and some bacteria such as staphylococci (although not used clinically for staphylococci). Ketoconazole also has some antiinflammatory effects, and some of its efficacy in treating dermatoses may be attributed to this action.[70]

Ketoconazole is absorbed well from the GI tract, but its absorption is favored in an acidic environment. Because feeding stimulates acid secretion, absorption is improved if ketoconazole is administered with food in small animals. Do not administer ketoconazole concurrently with drugs that inhibit acid secretion.

Ketoconazole is not recommended for the treatment of dermatophytosis or *Malassezia* spp. in cats because itraconazole is so much better tolerated. It is effective for the treatment of infections caused by *Histoplasma, Coccidioides*, and *Blastomyces* spp. It is less effective for *Aspergillus* infections. It has

been used alone to treat infections caused by *Coccidioides* and *Histoplasma*, but severe infections caused by *Blastomyces* spp. are first treated with amphotericin B.

Nausea, anorexia, and vomiting are the most common adverse effects. They usually are dose related and may be diminished by decreasing the dose, dividing the total dose into smaller doses, and administering each dose with food.

Enilconazole use is covered in Chapter 32 and is reviewed extensively by Moriello.[71]

Itraconazole

Itraconazole (Sporanox7) is one of the most popular triazole antifungal drugs. Triazoles are similar to imidazoles, except that they have three nitrogen atoms on the five-member azole ring. One of the differences between triazoles and imidazoles is that triazoles lack affinity for some of the cytochrome P-450 enzymes in animals, which results in fewer endocrine effects.

Itraconazole is considerably more potent than ketoconazole (5 to 100 times more active) and is associated with fewer side effects. It has no endocrine effects compared with ketoconazole. Itraconazole is highly protein bound in plasma, and strong binding occurs to keratin, which produces drug concentrations in skin that persist 2 to 4 weeks after cessation of drug therapy. It may be excreted into the sebum, which increases the concentrations in skin. This allows for pulse-therapy for some diseases, which is described in the dosing section. *Histoplasma, Cryptococcus*, and *Blastomyces* spp. are highly susceptible; *Candida, Aspergillus,* and *Penicillium* spp. are less sensitive. Itraconazole also has been used to treat cutaneous leishmaniasis because the *Leishmania* organism has ergosterol in high concentrations in its cell wall. Itraconazole probably is better tolerated in cats than ketoconazole. Nevertheless, toxic reactions still are possible. Because most adverse effects are dose-related, the clinician is advised to lower the dose in animals in which adverse effects are observed. One report indicated that administration of itraconazole resulted in dose-related GI effects of anorexia and vomiting in cats.[72]

Doses in cats vary from 5 to 10 mg/kg q24h PO for at least 56 days to 10 mg/kg q24h for 28 days, followed by pulse therapy of 1 week on, 1 week off. Lower doses of 1.5 to 3 mg/kg q24h for cycles of 15 days at a time also are used.

The recent addition of a commercially available registered formulation for cats has helped treat cats in Europe. Itraconazole (Itrafungol) 10 mg/mL oral solution is registered for use in cats to treat dermatophytosis. Although not registered in the United States, this formulation is identical to the Sporanox oral liquid marketed in the United States. The treatment schedule consists of 5 mg/kg PO q24h for three 1-week cycles. After each week of treatment, it should be followed by a week without treatment. This schedule has been evaluated in cats and maintains drug concentrations in hairs during the nontreatment phase.[73]

Fluconazole

Fluconazole has a similar spectrum as other azoles but is less active against *Aspergillus* spp. Toxicity is less than for ketoconazole. It has been used in human beings to treat blastomycosis, histoplasmosis, and cryptococcal meningitis. In animals it has been used to treat aspergillosis, blastomycosis, dermatophytosis, and cryptococcal infections.

Fluconazole has different solubility characteristics than ketoconazole and itraconazole, and is absorbed well regardless of diet and other co-administered drugs that might interfere. Fluconazole absorption is complete in animals. Fluconazole tablets and oral suspension (10 mg/ml) are absorbed well and the oral dose is similar to the IV dose. Because fluconazole is water-soluble, it is more amenable to compounding than itraconazole.

The advantage of fluconazole probably lies in its ability to produce higher CSF concentrations than ketoconazole or itraconazole, and therefore may be useful for treating mycotic meningitis. In cats, fluconazole has a long half-life of 25 hours, with good absorption and distribution to the CSF and aqueous humor.[74] Fluconazole has no effect on endocrine activity, and it has less of a tendency to cause drug interactions in human beings compared with itraconazole. It is unknown whether this is true in cats.

For cats with cryptococcosis, clinical studies have shown a benefit from a dose of 100 mg/cat/day PO in one or two divided doses. Other reported doses are 2.5 to 5 mg/kg q24h.[75] Pharmacokinetic studies support a dose of 50 mg/cat per day.[74]

ANTIMICROBIAL DRUGS FOR CATS

General use of antimicrobial drugs has been described for dogs and cats in other references.[76] The same principles that apply to dogs also apply to cats. However, some exceptions exist for fluoroquinolones. Because fluoroquinolones are an important group of drug for cats and have unique toxicities, more detail is provided below for these drugs.

Fluoroquinolones

The fluoroquinolones approved in the United States for animals include enrofloxacin, marbofloxacin, difloxacin, and orbifloxacin. In the United States, all of these drugs are approved for dogs; orbifloxacin, marbofloxacin, and enrofloxacin are approved for cats. Enrofloxacin 100 mg/ml injection and danofloxacin (A180) injection are approved for cattle. These should not be injected in cats because they may cause injection-site lesions. A topical formulation of enrofloxacin and silver sulfadiazine (Baytril Otic) is registered for treating otitis externa in dogs, but its use in cats has not been reported. Several other fluoroquinolones are approved for use in human medicine (e.g., ciprofloxacin, lomefloxacin, enoxacin, ofloxacin), but their use has been limited in veterinary medicine, except for ciprofloxacin.

The mechanisms of action and important pharmacological properties have been reviewed elsewhere.[77] The advantages of these drugs are (1) spectrum of activity that includes most gram-negative bacteria and many gram-positive bacteria, including staphylococci, (2) oral and injectable administration, and (3) good safety profile. Important deficiencies in the spectrum of activity include gram-positive cocci, especially enterococci (*Enterococcus faecalis* and *Enterococcus faecium*), and anaerobic bacteria. The newest generations of fluoroquinolones (referred to by some authors as the third-generation quinolones) include trovafloxacin, grepafloxacin, gatifloxacin, sparfloxacin, and moxifloxacin. Two of these, trovafloxacin and grepafloxacin, already have been discontinued for use in human beings because of adverse effects (abnormal cardiac rhythms and hepatic injury). The new generation of fluoroquinolones,

with substitutions at the C-8 position (e.g., C-8 methoxy), have an advantageous broader spectrum that includes anaerobic bacteria and gram-positive cocci. The difference in spectrum of activity is caused largely by increased activity against the DNA-gyrase of gram-positive bacteria, rather than activity against topoisomerase IV, which is the target in gram-positive bacteria for the older quinolones.[78,79] Premafloxacin, a veterinary third-generation, was tested for its potential in veterinary medicine[80] but has been discontinued. Pradofloxacin has been evaluated in dogs and cats, but the experience thus far is limited to a few research abstracts.[81,82] The latter drug is promising because it was more active than other fluoroquinolones against bacterial isolates from dogs and cats.[81] Moxifloxacin (Avelox), is a human drug of this group and has been used on a limited basis for treatment of infections in cats (10 mg/kg PO q 24h) caused by bacteria that have been refractory to other drugs (unpublished observations).

Of the currently available fluoroquinolones, all have a similar spectrum of activity, but they may vary in potency. Against some gram-negative bacilli, especially *Pseudomonas aeruginosa*, the human drug ciprofloxacin is more active than veterinary quinolones. Enrofloxacin is converted partially to ciprofloxacin by metabolism and comprises approximately 10 per cent of the peak fluoroquinolone concentration in cats.[77] Orbifloxacin and marbofloxacin have few or no active metabolites, but they are well absorbed and achieve higher plasma concentrations after equivalent doses compared with enrofloxacin. Generally, all of the veterinary fluoroquinolones attain good concentrations in tissues, with tissue:plasma concentration ratios approaching, or greater than, 1.0.

Fluoroquinolones have had a good safety record after administration to animals. Central nervous system effects, such as seizures, may occur at high doses but are rare. In young animals, especially dogs and foals, arthropathy of the developing cartilage is possible, leading to joint injury and lameness. However, this has not been reported in kittens.

Recently, blindness in cats caused by fluoroquinolones has attracted attention. This concern was precipitated by a report by Gelatt, et al[83] in which retinal degeneration was associated with enrofloxacin administration. This was followed by a letter to veterinarians[84] from the manufacturer in which their studies on ocular toxicosis from enrofloxacin were described and new dose labeling was announced. No published reports indicate that the other fluoroquinolones approved for use in cats (orbifloxacin, marbofloxacin) have been associated with blindness, nor do any reports exist of ocular toxicosis in other animal species caused by enrofloxacin. In the report by Gelatt, et al,[83] all cats were domestic shorthairs. Ages ranged from 3 to 16 years, but the average was 8.8 years. The most common ophthalmological abnormalities were mydriasis, lack of menace reflex, and poor pupillary light reflexes. Some cat owners noticed acute blindness. Ocular lesions were limited to the retina and included increased tapetal reflectivity and attenuation of retinal blood vessels. The doses varied from 4.6 mg/kg/day to 54 mg/kg/day, but the dose of 5 mg/kg/day was exceeded in all but one of the cats in the report. Older cats also tended to be affected by lower doses than the younger cats.

In studies performed by the manufacturer, enrofloxacin was administered to cats at doses of 0, 5, 20, and 50 mg/kg for 21 days (eight cats per group). No adverse effects were observed in cats treated with 5 mg/kg/day of enrofloxacin. However, the administration of enrofloxacin at 20 mg/kg or greater caused salivation, vomiting, and depression. At doses of 20 mg/kg or greater, mild to severe fundic lesions occurred on ophthalmological examination, including changes in the fundus and retinal degeneration. Electroretinograms also were abnormal, including blindness.

Before these reports, the labeled dose for enrofloxacin (Baytril) for use in cats, according to the "professional flexible label" guidelines, had been 5 to 20 mg/kg/day. Because the blindness has been associated with high dose, the manufacturer now has limited the dose to 5 mg/kg/day in cats, which has decreased the incidence of drug-induced ocular problems.

Besides enrofloxacin, the other fluoroquinolones registered for use in cats are orbifloxacin (Orbax) and marbofloxacin (Zeniquin). The current approved dose of orbifloxacin for cats is 2.5 to 7.5 mg/kg/day. In a published abstract,[85] orbifloxacin oral liquid was administered to cats at 0, 15, 45, and 75 mg/kg for at least 30 days (eight cats/group). This represents 6, 18, and 30 times the lowest label dosage. No ocular lesions were observed in any cats treated with 15 mg/kg. At the higher doses (18 and 30 times dose), tapetal hyperreflectivity in the area centralis and minimal photoreceptor degeneration occurred.

When marbofloxacin was administered to cats at 5.55, 16.7, and 28 mg/kg, representing 2, 6, and 10 times the lowest label dose, no ocular lesions were present after 6 weeks (manufacturer's data). At 55.5 mg/kg (10 times the lowest label dose) for 14 days, no lesions occurred from marbofloxacin.

Clinical Use of Fluoroquinolones in Cats

Fluoroquinolones are indicated for the treatment of susceptible organisms in cats. Infections not listed on the manufacturer's label that have been treated with these drugs include *Chlamydia* spp., *Mycoplasma* spp., and *Pseudomonas aeruginosa*. The use of fluoroquinolones for treatment of *P. aeruginosa* should be guided by a susceptibility test result (see Chapter 38). Fluoroquinolones may be active against *P. aeruginosa,* but usually MIC values are higher than against other gram-negative organisms. Subsequently, in administration of a fluoroquinolone to treat *P. aeruginosa,* the high-end of the dose range is suggested (however limited to 5 mg/kg for enrofloxacin). Of the currently available fluoroquinolones (human or veterinary drugs), ciprofloxacin is the most active against *P. aeruginosa*. Its use is discussed below.

Although no data are available for *Pseudomonas* spp. cultured from cats, many pseudomonads cultured from dogs can be resistant. *Pseudomonas* resistance to fluoroquinolones was demonstrated in a study of ear infections in dogs in which 65 per cent and 87.5 per cent of the *Pseudomonas* spp. from horizontal and middle ear, respectively, were resistant to enrofloxacin.[86] In another study,[87] 52 per cent of *Pseudomonas* spp. from chronic otitis externa in dogs were sensitive to enrofloxacin, and 91.3 per cent were sensitive to marbofloxacin. In a different study,[88] approximately one half of the strains of *Pseudomonas* spp. were sensitive, and half were resistant using an agar-disk-diffusion (ADD) test.

Fluoroquinolones were less active against *Pseudomonas* spp. than other organisms tested, with MIC values ranging from 1 to 8 µg/ml; marbofloxacin had the lowest MIC of those tested.[89] From the field isolates, the MIC_{90} for *Pseudomonas* spp. ranged from 4.0 µg/ml (marbofloxacin) to 16 µg/ml (orbifloxacin) but was in the "resistant" range for all drugs. In an in vitro comparison from our laboratory[90] of the veterinary

fluoroquinolones and the human drug ciprofloxacin against an ATCC strain of *P. aeruginosa*, the MIC was lowest for ciprofloxacin (0.52 µg/ml), followed by marbofloxacin (2.1 µg/ml), enrofloxacin (4.4 µg/ml), and orbifloxacin (10.0 µg/ml).

We encourage veterinarians to consider veterinary-labeled fluoroquinolones in their patients first because safety and efficacy data have been derived specifically for animals before FDA approval. Ciprofloxacin is a human drug, not registered for animals. However, veterinarians can use it legally, as long as it is not administered to food animals. The use would be considered extra-label and subject to other extra-label restrictions (e.g., a veterinarian-client-patient-relationship [VCPR] needs to be established). Since ciprofloxacin became available in a generic formulation, interest has been aroused in its use in animals because of a difference in cost. In cats, it was safe when administered at 100 mg/kg without producing ocular toxicity.[91] When cats were given ciprofloxacin orally, oral absorption was low (22 to 33 per cent) and it would not have been effective for gram-positive bacteria even at 10 mg/kg.[92] At 10 mg/kg q12h, it was able to reach therapeutic targets against susceptible gram-negative bacteria. Other fluoroquinolones have near complete bioavailability in cats.

Injectable ciprofloxacin is available in a human formulation, usually 10 mg/ml (in sterile water) or 2 mg/ml (premixed with 5% dextrose). For human beings, it is recommended to dilute the concentrated form to 1 to 2 mg/ml before use as an intravenous solution and infuse the final solution over 60 minutes. Administration protocols have not been evaluated in dogs or cats. It should not be infused concurrently with other medications (e.g., in a piggy-back) because inactivation may occur. Solutions of 0.5 to 2 mg/ml retain potency up to 14 days when stored.

BEHAVIOR DRUGS

Tricyclic Antidepressants (TCAs)

These drugs take their name from the tricyclic ring structure. Most drugs in this class used in veterinary medicine are tertiary amine tricyclics. (Secondary amine tricyclics include drugs such as amoxapine, nortriptyline, and desipramine.) All of the TCA drugs discussed here share similar properties. For people, they have been used primarily to treat disorders associated with anxiety and depression and for obsessive-compulsive disorder (OCDs). These drugs have been used in cats to treat aggression, inappropriate urination, OCDs, and anxiety syndromes. Clomipramine has been more effective for treatment of OCDs in dogs, but has not been evaluated in cats.

Imipramine is the prototype of this group. One drug in this class, clomipramine, appears to be the most specific for OCDs (perhaps because it is more specific for serotonin reuptake). These drugs were reviewed in a recent paper.[93]

All drugs in this group share common pharmacological actions. The efficacy is related to potentiation of serotonin and/or epinephrine. The TCAs block reuptake of norepinephrine and 5-hydroxytryptamine (5-HT, serotonin) in the nerve terminals of the CNS. They also block adrenergic (α_1), histaminergic (H-1), and muscarinic receptors to varying degrees. Variation in response and in adverse effects among drugs is related to relative differences in action among them on each of these neurotransmitters. For example, secondary amines of this class (nortriptyline and desipramine) are relatively selective for inhibiting reuptake of norepinephrine, but the tertiary amines (clomipramine, amitriptyline, imipramine) inhibit reuptake of both norepinephrine and 5-HT.

Clomipramine may be the most selective of this group for inhibiting reuptake of 5-HT. The theory to explain the effects of these drugs is that an imbalance of the biogenic amine neurotransmitters in the brain is responsible for abnormal behavior. These drugs restore the neurotransmitters to the appropriate level. Most experts agree that the clinical effects on behavior may not be evident until 2 to 4 weeks and as long as 6 weeks after initiating treatment. This lag time for a clinical response may be caused by a gradual change in receptors that is not evident after a single dose. Many clinicians initiate therapy at the lowest listed dose and increase after 4 weeks if a desired clinical response is not observed. No well-controlled studies are available to show that the TCAs are different in efficacy. They may differ markedly, however, in the incidence of side effects.

Side effects are attributed to their ability to block α-adrenergic receptors, muscarinic receptors, and histamine receptors. Clinical signs reported are sedation, dry mouth (seen often in animals as polydipsia), increased heart rate, tachyarrhythmia, urine retention, constipation, and (in human beings) hypotension. Specific effects on receptors are listed below.

Histamine Blockade

Tricyclic drugs have the ability to block histamine receptors but differ in their affinity. Blockade of histamine receptors helps explain their sedative effects and may explain the benefit (although controversial) for treating allergic disorders such as atopic dermatitis in animals. The TCA with the highest antihistamine activity is doxepin. Trimipramine and amitriptyline also have antihistamine activity.

Muscarinic (Cholinergic) Receptor Blockade

These drugs have the ability to block muscarinic receptors. Thus they have atropine-like effects but vary in their antimuscarinic potency. Amitriptyline has the most potent antimuscarinic action. The antimuscarinic action explains the side effects of dry mouth (xerostomia), rapid heart rate, constipation, and urine retention. Because of this action, these drugs should not be used in combination with other antimuscarinic drugs.

Clomipramine (Anafranil, Clomicalm)

Clomipramine may have more of a selective action on inhibition of serotonin reuptake than other drugs in this class. This action may relate to its efficacy for the treatment of OCDs in people,[94] which also has been a use in dogs and cats. It has been investigated more than most of the other TCAs in animals. Published reports also showed that clomipramine was effective in dogs with canine lick granuloma.[95,96] Dogs appear to tolerate clomipramine better than human beings. The most common side effects have been sedation and weight gain. Less common effects are the antimuscarinic effects such as xerostomia.

The pharmacokinetics have been reported for dogs, in which clomipramine is metabolized more quickly than in people and clearance is higher in dogs. For example, the half-life in dogs is 5 hours, but in human beings, in excess of 24 hours. These differences account for a change in dose and expectations for

adverse effects compared with dogs. However, the pharmacokinetics have not been reported for cats. The most effective dose for cats being treated for urine spraying is 0.25 to 0.5 mg/kg PO q24h.[97,98] Doses administered clinically to cats for other indications have been 0.5 mg/kg q24h (most often 2 mg/cat q24h). Sedation was the most frequently reported side effect.[98] Weight gain also was noted in treated cats, but only at higher doses.

Amitriptyline has been one of the most frequently used TCAs in veterinary medicine. In people, nortriptyline is an active metabolite. Amitriptyline is used primarily for the treatment of anxiety and has been combined with other forms of behavior modification.

Amitriptyline can have pronounced anticholinergic side effects. Unpleasant taste for some animals and sedation are some of the cited problems. Because of difficulty in oral administration of medication to cats, a transdermal gel (PLO gel) of amitriptyline has been examined. However, the preliminary results of a study in cats showed that the transdermal application did not produce effective concentrations[19] (see Chapter 18).

One of the uses of amitriptyline in cats has been to treat urinary tract disease. It has been used to control inappropriate urination in cats with lower urinary tract disease caused by idiopathic interstitial cystitis[99] (see Chapter 47). The specific mechanism whereby it helps control urinary tract disease in cats is not known. Among the possible actions are the antimuscarinic and ß-adrenergic effects to allow more bladder filling. The efficacy also may be caused by an analgesic effect or simply altering the cat's behavior. The most common dose for this effect is 5 to 10 mg per cat, given once in the evening. The efficacy may require as long as 4 weeks.

Selective Serotonin Reuptake Inhibitors (SSRIs)

This group of drugs has grown in popularity in human and veterinary medicine. The most popular of this group is fluoxetine (Prozac). These drugs were reviewed in a recent paper.[93]

The mechanism of action of SSRIs is to inhibit reuptake of serotonin (5-HT) in a selective manner. The effect on behavior is caused by inappropriate levels of 5-HT in the brain. This leads to abnormal behaviors observed such as aggression, depression, and OCDs. As compared with the TCAs, SSRI drugs do not produce significant sedative, anticholinergic, or cardiovascular effects because of their specificity for 5-HT compared with other neurotransmitters. Also, they have a higher margin of safety and an overdose is less hazardous.

Selective serotonin reuptake-inhibitors have been used for OCDs in animals, anxiety, treatment of fears and phobias, and aggression. Some evidence supports their use for treatment of neuropathic chronic pain. Fluoxetine has even been shown to have antimicrobial effects (at high concentrations). Veterinary use of these drugs is based on some clinical studies and some anecdotal accounts. Clinical trials using double-blind crossover comparisons in animals have documented the effect for OCD in dogs.[95] Fluoxetine has been more effective than other drugs in reduction of licking in dogs with lick granulomas. However, limited experience is reported for cats. One report exists of successful treatment of psychogenic alopecia in a cat with fluoxetine.[100] Another report showed that fluoxetine (1 mg/kg PO q24h) and clomipramine (0.5 mg/kg PO q24h) were equally effective for reducing urine marking in cats.[97]

As with the TCAs, a lag period exists from initial dose to clinical effects, which may require 4 weeks or more. The explanation for the lag period is because of a gradual change in receptors, or because of their characteristically long half-lives (or perhaps the long half-life of the active metabolites). For drugs with long half-lives, it may require several days for steady-state blood concentrations to accumulate.

In general, the side effects from SSRIs are mild and not nearly as common or as serious as with the TCAs. Changes in appetite have been noted, especially a decreased appetite that apparently is more prominent in cats (unpublished observations). Other gastrointestinal effects such as diarrhea and vomiting have been seen. High doses of fluoxetine have caused tremors and mydriasis in cats. Some behavioral changes have been observed, such as increased sleeping and increased excitement. Increased agitation and irritability also have been observed. SSRI drugs are safer than TCAs in pregnant animals.

FLUOXETINE (PROZAC). Fluoxetine has received attention for treatment of various behavioral disorders in small animals. In human beings, it is approved for treatment of depression and OCD. The half-life of fluoxetine in people is several days and may be as long as 10 to 20 days. As a result, it may take at least 2 weeks before steady-state plasma concentrations are achieved. A lag-time of 1 to 2 weeks is common before beneficial effects occur when used in people. The half-life of fluoxetine in cats was reported to be 47 hours, with the half-life of the active metabolite norfluoxetine 55 hours.[15]

Fluoxetine is available in 10-mg to 20-mg capsules and a 4-mg/ml oral liquid. For cats the most common dose is 1 mg/kg q24h. Because cats may be difficult to medicate orally, a transdermal application has been attempted. Transdermal absorption was 10 per cent relative to the oral dose.[15] The transdermal dose to achieve concentrations equivalent to an oral dose was 10 mg/kg in cats applied to the skin of the ear pinna. Repeated applications caused dermal irritation.

PAROXETINE (PAXIL). Paroxetine has been used in animals but has not been as popular as fluoxetine. Compared with fluoxetine, it is a weak inhibitor of norepinephrine and dopamine uptake. It has a shorter half-life than fluoxetine and a more rapid onset of clinical effects. Some veterinarians have found it more convenient than fluoxetine to administer to cats because of the tablet form, and animals may tolerate the taste better than other SSRIs. Doses reported for cats are ⅛ to ¼ of a 10-mg tablet q24h (approximately 1.25 to 2.5 mg/cat q24h). It is available as tablets of 10, 20, 30, and 40 mg.

BUSPIRONE (BUSPAR). Buspirone is believed to act by blocking release of serotonin by binding to presynaptic serotonin receptors. It also acts as a dopamine agonist. It has been used as an antianxiety agent for people. In animals, its most common use has been for the treatment of inappropriate urination in cats ("urine spraying"). For treatment of urine spraying in cats, one study suggested that a lower relapse rate occurred after treatment with buspirone as compared with treatments with diazepam or megestrol acetate.[101] When buspirone has been effective for urine spraying, a positive response occurred within the first week, but for treating other behavior problems a lag time of 2 to 4 weeks can be expected.

Buspirone has fewer side effects compared to other antidepressant drugs. Some cats showed increased aggression to other cats, other cats showed increased affection to their owners.

Doses used in cats have ranged from 2.5 to 5 mg/cat PO q24h as an initial dose, and increased to 2.5 to 7.5 mg/cat PO

q12h. For urine spraying, treatment usually is continued for at least 8 weeks. It is available as 5-mg and 10-mg tablets. Because of difficulty in administering oral medication to cats, a transdermal gel (PLO gel) of buspirone has been evaluated. However, the preliminary results of a study in cats showed that the transdermal application did not produce effective concentrations.[19]

SEDATIVES AND ANALGESIC DRUGS

Diazepam

Diazepam is a commonly used sedative and behavioral modification drug in cats. Published reports describe acute hepatic necrosis and liver failure in some cats that received oral diazepam. In one report, 10 cats died or were euthanized as a result of this reaction.[102] One cat that survived required intensive therapy. In another report,[103] six cats were described with severe hepatic necrosis as a result of diazepam administration. All six cats died. Affected cats were lethargic, depressed, and anorectic. Clinicopathological changes include marked increases in hepatic enzymes, especially ALT and AP, and increases in bilirubin. The hepatic enzymes GGT and AST may be elevated. Liver injury was characterized as mixed (cytotoxic and cholestatic) with hepatic necrosis, loss of hepatocytes, and suppurative cholangitis. It is believed to be an idiosyncratic reaction.

Opiates

The desired effects when opiates are administered to a painful animal are analgesia, euphoria, relief of anxiety, and sedation. However, dysphoria and excitement can occur in some animals. These dysphoric reactions may result in discontinuation of the drug and switching to another analgesic. Severe reactions should be reversed with administration of naloxone. In people, dysphoric reactions are more common with opiate mixed agonists or agonists/antagonists such as butorphanol as compared with pure agonists such as morphine or oxymorphone. Cats are particularly susceptible to dysphoric reactions and excitement from administration of opiates. The explanation for the sensitivity in cats is not completely understood but is believed to be related to a difference in the distribution of opiate receptors in the feline central nervous system. To prevent these problems, sedatives and neuroleptic drugs (e.g., acepromazine) often are administered before opiates in cats. Also, when pure agonists such as morphine or oxymorphone are administered to cats, the doses usually are lower than for dogs. When opiate agonists/antagonists have been administered to cats in clinical studies, signs of dysphoria or excitement have been rare or nonexistent.

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Chapter 32

RECENT RESEARCH ON DERMATOPHYTOSIS*

Karen A. Moriello and Douglas J. DeBoer

This chapter focuses on new, important information regarding feline dermatophytosis. For more information about all aspects of feline dermatophytosis, the reader is referred to recently published discussions for more information.[1,2]

TRICHOPHYTON INFECTIONS, POSSIBLY UNDERRECOGNIZED IN CATS

The most commonly isolated dermatophyte pathogen from cats with dermatophytosis is *Microsporum canis*. Less commonly isolated pathogens include *Microsporum gypseum* and *Trichophyton* spp. *M. gypseum* is a geophilic dermatophyte that is most likely to be found in feral and/or outdoor cats.

Some emerging clinical evidence suggests that *Trichophyton* spp. infections may be an underdiagnosed cause of skin disease in cats.

Worldwide, the dermatophyte isolated most commonly from cats is *Microsporum canis*. It also is clinically a pleomorphic disease in presentation (Table 32-1). In our recent experience, we have found evidence to suggest that *Trichophyton* spp. may be important pathogens in cats. In a collaborative study with a large Midwestern animal shelter that admits more than 4000 cats annually, preliminary data from year 1 of a multiyear study suggest that *Trichophyton* spp. infections may be an underrecognized skin infection. In this study, all cats are screened for dermatophytosis with physical examination, Wood's lamp examination, and toothbrush fungal culture technique.[2a] At the start of the study in the early summer, *M. canis* was the predominant pathogen isolated from clinically affected cats or mechanical carriers. Beginning in the late fall and continuing throughout the winter, *M. canis* isolation dropped to almost zero and was recovered rarely from cats entering the shelter. This was somewhat expected, because the total number of kittens and juveniles admitted to the shelter decreased. An unexpected finding was that *Trichophyton* spp. infections were now the primary pathogen isolated from cats. Before the sharp decline in *M. canis* isolates, this organism had not been isolated from cats entering the shelter. This trend continued until late spring when *M. canis* again became the predominant pathogen. Of clinical interest was that the majority of *Trichophyton*-infected cats had lesions limited to their ears, consisting of pruritus and mild scales and crusts adhered to the ear margins. The lesions were mild and easily overlooked; at their worst they resembled mild insect bite hypersensitivity. Furthermore, if left untreated, cats did not develop generalized dermatophytosis.

The reason for this seasonal occurrence of *Trichophyton* spp. infection is unclear. These infections simply may have been missed during the warm weather months. *Trichophyton* spp. fungi grow slowly and require warmer incubation temperatures. Perhaps this pathogen was missed because of contaminant overgrowth or, in the possible case of dual infections, *M. canis* dominated the plate and the second pathogen was never isolated. Another possible explanation is the characteristics of the cat population surrendered to the shelter. Early in summer and fall, the majority of cats were young, and during the winter the population was predominantly older cats, strays, or feral cats. *Trichophyton* spp. are common in large animals and the natural reservoir for infection is rodents. Exposure may be from contact with large animals, rodents, or farms. In the Midwest during winter, stray or feral cats frequently are live-trapped by farmers, landowners, and other concerned individuals to prevent them from dying as a result of exposure to the elements. The cats surrendered to the shelter in the winter may have selected for a population of cats with increased exposure to *Trichophyton* spp. Another reason the seasonal occurrence may not have been noted previously is that these infections were markedly less severe than *M. canis* infections, and limited in

*Sections of this chapter were modified with permission from the following publications:
Moriello KA: Treatment of dermatophytosis in dogs and cats: review of published studies. Vet Dermatol 15:99-107, 2004.
Moriello KA: Feline dermatophytosis symposium, Parts 1-4, Vet Med 98:844-891, 2003.

Table 32-1 | **Clinical Signs and Differential Diagnoses of Dermatophytosis**

Dermatophytosis in cats can present with any combination of the following signs:
Pruritus: none to severe
Hair loss: focal, multifocal, or generalized
Erythema
Crusting and scaling: mild to severe
Comedones
Hyperpigmentation
Paronychia

Dermatophytosis is pleomorphic in its presentation, and it is a reasonable differential diagnosis for any of the following reaction patterns:
Paronychia
Chin acne
Unilateral eosinophilic lip ulcers
Eosinophilic plaques
Symmetrical alopecia or overgrooming
Facial pruritus
Pruritic pinnae
Miliary dermatitis-like lesions
Granulomatous lesions: well-circumscribed, ulcerated nodular lesions
Persistent facial fold dermatitis
Periocular pruritus
Widespread pruritic, exfoliative erythroderma
Severe exfoliative crusting
Seborrheic otitis externa

their lesion distribution for unknown reasons. Studies are continuing to determine if this seasonal occurrence is unique to the geographical region. At this time, whether these infections are unique to stray/shelter populations is unknown.

STUDIES OF FUNGAL CULTURE MEDIA AND INCUBATION TEMPERATURES

Many fungal culture media are available commercially for in-house laboratory use. A recurrent question is, "What is the best medium?" In one unpublished study (abstract), five different fungal culture media were evaluated.[3] The investigators compared Rapid Sporulation Medium (RSM) (Bacti-Labs, Mountain View, CA), two commercial brands of Sabouraud's dextrose agar, and two commercial brands of dermatophyte test medium (DTM) media for growth, sporulation, and identification characteristics of *M. canis*. The study found all five diagnostic media to be adequate for growth and identification of *M. canis*. One of the media, RSM, believed to speed sporulation, did not produce macroconidia faster than the other media. Based on the findings of this study, clinicians should consider cost, shelf-life, and ease of inoculation as the most important criteria for selection of culture media in clinical practice.

In another study examining the efficacy of a commercial fungal culture medium developed for animals (Rapid Vet D, dms Laboratories, Inc. Flemington, NJ), the authors found that incubation temperature may be an important but overlooked factor in sporulation. Current recommendations suggest that fungal cultures be incubated at "room temperature." This is a vague recommendation and "room temperature" can vary considerably depending upon the outside ambient temperature. In this study, the authors found that increased incubation temperatures (24° to 27° C or 75° to 80° F) resulted in more rapid sporulation of fungi.[4] This is an important finding because "room temperature" in many veterinary clinics is rarely this warm in the winter and clearly nowhere near this ideal temperature in the summer when air conditioning is used. In our experiments with temperature and fungal culture sporulation, less-than-optimal temperatures resulted in colony growth that grossly resembled *M. canis,* but microscopic examination revealed only unsporulated hyphae. This was true for DTM and Sabouraud's dextrose agar.

Inadequate incubation temperatures may be the key reason why clinicians have difficulty getting fungal cultures to sporulate. Increasing the optimum incubation temperature can be achieved easily by putting cultures in a standard incubator or light bulb incubator. If the clinic does not have an incubator, a do-it-yourself "fungal culture only" incubator can be constructed with a sheet of glass, a floor heating element for reptile cages, a plastic box with a lid, and a digital fish tank thermometer. The heating element is adhesive and adheres to the underside of the glass. The fungal cultures are incubated in a plastic box placed over the glass and the temperature range monitored with the fish tank thermometer. Regardless of the incubator system employed, the premature dehydration of the media is an important problem. This can be solved easily by placement of a small beaker of water in the incubator system.

FIELD STUDIES OF ENVIRONMENTAL CONTAMINATION

In a recent study, investigators sampled the air and the physical environment of the homes of 30 animals infected with *M. canis* (9 dogs and 21 cats).[5] Contact plates were used to sample environmental surfaces, and the air was sampled with use of a Sas-Super-100 Air Sampler. All of the homes with cats were found to have environmental and air contamination, but only four of nine homes of dogs were contaminated. The most heavily contaminated homes had infected kittens living in them. In addition, people were infected in eight households. All of these homes had cats; no infected people were found in homes with infected dogs.

In another environmental study, 400 samples from the floors of 50 veterinary clinics were sampled with use of contact plates.[6] In this study, more than 11 different pathogenic fungi were found in the environment, presumably from patients entering the facility. In previously published studies, we reported on severity of environmental contamination of rooms housing infected cats in a biohazard containment facility where the cats were allowed to roam free. The rooms were cleaned once daily by sweeping, and bedding and debris were removed; they were disinfected once weekly. Within 1 hour of cleaning, positive fungal cultures were obtained from the rooms. The naturally infective state of *M. canis* is the arthrospore, formed from segmentation and fragmentation of fungal hyphae. These infective spores get into the environment when infected hairs break off and are shed into the environment. The spores are very small and can be carried on air currents and dust particles.

These studies highlight the importance of any reasonable efforts to minimize contamination of the environment. Infective spores in the environment are a significant problem because they pose risk of infection to susceptible animal and

Table 32-2 | **General Recommendations Regarding Treatment Endpoint***

Treatment Endpoint: The endpoint of treatment is twofold: a mycological cure and decontamination of the environment.
MYCOLOGICAL CURE: KEY CLIENT EDUCATION POINTS
Cats attain a clinical cure before a mycological cure.
A mycological cure is defined as "2 to 3 negative toothbrush fungal cultures at weekly or biweekly intervals."
Two negative cultures usually are sufficient in single cat situations.
Three negative cultures are the preferred criteria for mycological cure when multiple cats are involved.
DECONTAMINATION OF THE ENVIRONMENT: KEY POINTS
Infective material can remain viable in the environment for long periods of time under optimum conditions of temperature and humidity.
Infected hairs and spores are shed into the environment by cats during the entire treatment period.
Contact with infective material increases the risk of reexposure, reinfection, and prolonged treatment periods.
Decontamination of the environment must involve aggressive and thorough "gross cleaning," and regular intervals of disinfectant application.
The more cats involved in the outbreak and the longer the treatment period, the longer decontamination periods last.

*Modified and adapted for publication in this chapter from Moriello KA: Treatment of dermatophytosis in dogs and cats: review of published studies. Vet Dermatol 15:99-107, 2004; Moriello KA: Feline dermatophytosis symposium parts 1-4. Vet Med 98:844-891, 2003.

human hosts. Furthermore, contaminated environments can complicate treatment protocols because toothbrush cultures cannot distinguish between actively infected cats and cats mechanically carrying spores on their hair coat. A contaminated environment and/or inadequate decontamination procedures can lead directly to increased times to cure, that is, endpoint of therapy (Table 32-2). Clipping of the hair coat, often a highly heated issue between clients and veterinarians, is one of the simplest ways to minimize gross contamination of the environment (Table 32-3).

STUDIES OF THE EFFICACY OF TOPICAL ANTIFUNGAL AGENTS*

A number of in vitro and in vivo studies have examined the efficacy of various topical antifungal agents.[7-18] In vitro studies involve the use of isolated infected hairs and/or spores. This technique is a novel and economical way to evaluate existing or new products with supposed antifungal activity. Several variations of the in vitro model have been described, but all involve exposing either mats of infected hair or isolated infected spores to known dilutions of various topical antifungal agents for known periods of time. After treatment, the infective material is cultured and viability of fungal spores is determined via routine fungal culture. The advantages of isolated infected hairs or spores for testing include removal of difficulties encountered when trying to treat live animals, guarantee of appropriate contact with the antifungal agent, and elimination of the problem of continued spore production on the host. Problems with this model include an inability to quantify and standardize the amount of infective material being tested, maceration of hairs causing the release of spores within hairs that can result in negative fungal cultures becoming "positive" after repeated soakings, and loss of material from stockinettes or other testing containers. Nevertheless, this technique has provided valuable information on the efficacy of various commonly used antifungal compounds and this testing method is a useful screening tool for potential commercial products.

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Ineffective Products

Captan, povidone-iodine, and chlorhexidine have been found consistently to be ineffective against *M. canis* in in vitro or in vivo studies. Chlorhexidine solution used as dip was evaluated as a sole topical therapy in a controlled study using an experimental *M. canis* infection model.[18] In that study, infected cats were dipped twice weekly for 150 days after the hair coat was clipped. At the end of therapy, no significant difference existed between the chlorhexidine treatment group and the controls. Chlorhexidine was found to be ineffective. These products are not recommended for use in cats with dermatophytosis.

Effective Products

Lime sulfur, enilconazole, miconazole, and bleach 1:10 have been shown to be antifungal in in vitro and/or in vivo studies. Fungicidal efficacy is not intended to imply that one application of any of these products is 100 per cent fungicidal. These products are fungicidal with repeated application.

Bleach

A 1:100 dilution of household bleach is recommended for household use. *It is not recommended for use as a topical antifungal agent on cats.* It is too irritating to be used safely on cats and is not licensed for use in animals as a topical agent. A dilution of 1:10 may present a human health hazard because of its potential for irritancy.

Lime Sulfur

Lime sulfur (LymDip, DVM Pharmaceuticals, Miami, Florida) has been found consistently to be antifungal in in vitro studies.[8,9,12] No published in vivo studies use lime sulfur as a sole agent; however, we have used it as sole therapy in numerous situations and have found it to be consistently effective. Furthermore, one author (Moriello) supervised the eradication of dermatophytosis from a pet store with more than 30 infected kittens and cats. Shortly after being consulted by the pet store owner, financial constraints resulted in lime sulfur being used as the sole therapy in the majority of cats. With appropriate environmental decontamination, all of the cats were treated twice weekly as a sole therapy until cultured negative two times at weekly intervals.

Lime sulfur used twice weekly (8 ounces/gal) is the preferred treatment when enilconazole is not available or licensed for use. Lime sulfur stains the hair coat of white cats yellow-

Table 32-3 | **Recommendations for Clipping of the Hair Coat***

ADVANTAGES OF CLIPPING THE HAIR COAT
Clipping of the hair coat removes infected hairs and minimizes continued shedding of hair fragments and spores into the environment.
Clipping of the hair coat helps minimize contamination of the environment.
Clipping of the hair coat makes the application of topical therapy easier and allows for more thorough penetration of the topical antifungal agent.
DISADVANTAGES OF CLIPPING THE HAIR COAT
Clipping of the hair coat may require sedation of the cat.
Clipping of the hair coat is time consuming.
Clipping of the hair coat may worsen the infection temporarily by causing microtrauma to the skin.
Clipping of the hair coat may result in the environment being contaminated if appropriate efforts to capture infected hairs and spores are not taken.
GENERAL RECOMMENDATIONS REGARDING CLIPPING OF THE HAIR COAT
Clipping of the hair coat is optimum in all cases of dermatophytosis but not necessary in every case.
Clipping of the hair coat should be part of the therapy program in any pet cat that lives with children, elderly people, or anyone with immunosuppression. Returning the cat to a culture-negative status as quickly as possible is important in these situations.
In short-haired cats with focal lesions, children's metal blunt-tipped scissors can be used to clip and remove infected hairs from around individual lesions. Clipping a wide margin around the lesion is important.
Clipping of the hair coat is a necessary part of therapy in short-haired cats with generalized dermatophytosis and in all long-haired cats with dermatophytosis, regardless of the severity of lesions. The hair coat should be clipped with a #10 electric clipper.
If the strain of *M. canis* is strongly fluorescent, a Wood's lamp can be used during treatment to monitor resolution of the infection and locate these hairs for removal.

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green. It can be irritating to mucous membranes, and cats should be prevented from grooming the wet solution. However, extensive experience with the use of this product in cats being treated in shelters has shown that adverse reactions and irritant reactions are rare. Clients (and cats) tend to dislike the odor, but this diminishes rapidly once the cat dries. Owners should wear protective clothing, gloves, and protective eyeglasses and apply the solution in a well-ventilated area. These protective clothing recommendations are partially to prevent contact reactions in the applicator, and also to protect owners from contracting dermatophytosis because physical contact with an infected cat may be greater during these treatment periods. Clients must *not* rinse this product off the hair coat.

Enilconazole Topical Solution

Enilconazole topical solution (Imaverol, Merial, Canada, 100 mg/ml) is effective against *M. canis*. At the time of writing, it is not available in the United States nor is it approved for use on cats. Enilconazole is available in the United States as Clinafarm EC, 0.2 per cent emulsion through poultry supply houses. This formulation is licensed for use as an environmental disinfectant. It has been used off-label in the treatment of dermatophytosis at a dilution of 55.6 ml/gal as a topical antifungal agent. Because of the efficacy of enilconazole in the treatment of canine and equine dermatophytosis, it has been the subject of a number of studies that have evaluated its safety and efficacy in cats.[14-16] In two studies, it was the sole therapy for dermatophytosis; cats required at least 10 weeks of twice weekly topical therapy before being cured, but fungal cultures were negative as early as 5 weeks into therapy.[14,16] Enilconazole was well tolerated by all of the cats, but may have been associated with hypersalivation, anorexia, weight loss, emesis, idiopathic muscle weakness, and slightly elevated serum alanine aminotransferase (ALT) concentrations. Long-haired cats comprised the majority of the cats in these studies.

Miconazole

Miconazole, as a sole agent or in combination with chlorhexidine (Malaseb, DVM Pharmaceuticals, Miami, Florida) has been shown to be an effective antifungal agent in in vitro and in vivo studies.[10,11,13,17,19] It was used twice weekly in the in vivo studies as an adjuvant to systemic therapy. The shampoo needs a contact time of 10 minutes, which is essential for a therapeutic effect. A miconazole rinse (Malaseb Rinse, DVM Pharmaceuticals, Miami, Florida) has been released recently and may be an alternative option to bathing. As with any product used in cats, especially when prolonged and/or frequent use is needed, care must be taken monitor the cats for evidence of irritant reactions.

STUDIES OF SYSTEMIC THERAPY OPTIONS*

Systemic therapy is the treatment of choice for feline dermatophytosis. The following is a summary of the findings of a number of experimental and field in vivo studies on the most commonly used systemic agents.[†]

Griseofulvin

Griseofulvin is a fungistatic antifungal agent that inhibits nucleic acid synthesis and cell mitosis metaphase by interfer-

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[†]References 11, 13, 15-17, 20-33.

ing with the function of spindle microtubules. Griseofulvin has variable absorption, and its absorption is enhanced by feeding it with a fatty meal or by formulations containing polyethylene glycol. This drug is teratogenic and should not be given to pregnant animals. Anecdotal reports exist of its interference with spermatogenesis and, true or not, it is best avoided in breeding males.[19] The most common adverse effects are anorexia, vomiting, and diarrhea, which can be managed by dividing the dose into twice-daily administrations. Bone marrow suppression and neurological side effects most likely are idiosyncratic reactions. Griseofulvin should not be used in cats that have feline immunodeficiency virus (FIV) infections, because severe neutropenic reactions have been observed in FIV-infected cats.[24] The most commonly used dose regimen is daily (griseofulvin microsize 50 mg/kg PO q24h or divided q12h, griseofulvin ultramicrosize 10 to 15 mg/kg PO q24h or divided q12h). Griseofulvin soon may be unavailable for use in veterinary medicine because it is being replaced rapidly by newer antifungal agents.

Itraconazole

This drug is the first choice of many clinicians for the treatment of feline dermatophytosis. Itraconazole is a triazole derivative that works by altering fungal cell membrane permeability through inhibition of ergosterol synthesis.[34] It is available in a 100-mg capsule or 10-mg/ml formulation (Sporanox, Jansen Pharmaceuticals). Recently, an itraconazole liquid formulation 52 mg/ml for cats (Itrafungol, Jansen Animal Health) has become available in Europe. At low doses it is fungistatic and at higher doses it is fungicidal. In general, itraconazole is well tolerated by cats at the doses used to treat dermatophytosis. Vomiting and anorexia are the most common adverse effects and, in our experience, are dose-related. Itraconazole's antifungal activity against *M. canis* has been documented in human beings and guinea pigs for some time and has been summarized previously.[19] Three studies involving multiple cat situations provide some interesting insights regarding effective flexible dosing schedules.[20,21,23] Based upon these studies, the following dosing regimens can result in a mycological cure *provided* that they are accompanied by concurrent clipping, topical therapy, and environmental decontamination procedures.

Daily dosing: Itraconazole 10 mg/kg PO q24h[21]
Combined continuous/pulse therapy: Itraconazole 10 mg/kg PO q24h for 28 days, and then on an alternate week regimen (1 week off and 1 week on)[23]
Short-term cycle therapy: Itraconazole 10 mg/kg PO q24h for 15 days, followed by fungal cultures 10 to 15 days post treatment. These cycles are repeated until the cats are cured.[20]

It is important to point out that Mancianti et al used a dose of 1.5 to 3.0 mg/kg orally q24h in their study.[20] We recommend a higher dose of itraconazole (5 to 10 mg/kg) because only 8 of 15 cats in that study were cured of dermatophytosis at that dose. The 15-day treatment cycles are a cost-effective strategy in multiple-cat situations provided that a higher dose is used. If this strategy is used, weekly cultures during treatment are recommended, and cats should remain isolated until a mycological cure has been established.

Terbinafine

Terbinafine is the "newest" systemic antifungal agent to be used in the treatment of dermatophytosis. It is an allylamine antifungal agent that suppresses the biosynthesis of ergosterol via inhibition of the fungal enzyme squaline epoxidase.[35] The drug is considered to be fungicidal against dermatophytes. Of the five recent reports of its use in the treatment of dermatophytosis in multiple cat situations, two report on different aspects of the same experimental infection.[22,25-29] In addition, this drug has been used in a recently completed study at the University of Wisconsin.[36] With respect to clinical use, the following are key points from these studies:

- Terbinafine must be used at a dose of 30 to 40 mg/kg PO q24h.
- Terbinafine at a dose of 30 mg to 40 mg/kg PO q24h results in significant concentrations in hair when compared with lower doses.
- Terbinafine (30 to 40 mg/kg PO) may be substituted for itraconazole in continuous/pulse or cycle therapy.
- Terbinafine appears to be equivalent to griseofulvin and itraconazole in the treatment of feline dermatophytosis.[22,36]
- Terbinafine is well tolerated by cats, with vomiting as the most common adverse effect.
- Increased serum ALT concentrations also may be noted.[25]

STUDIES OF CONTROVERSIAL THERAPIES

Lufenuron

Lufenuron is a benzoylphenylurea drug that disrupts chitin synthesis and is used for flea control. Chitin is a critical component of the outer cell wall of fungi, and drugs that disrupt chitin synthesis also may have antifungal activity. In 2000, a retrospective study suggested lufenuron treatment was associated strongly with recovery in a large number of dogs and cats with a variety of fungal infections, including dermatophyte infections.[30]

Since that report, the use of lufenuron has been a widely debated topic in the lay and veterinary literature and has been the focus of numerous anecdotal and published reports.[15,31-33] Two reports exist of controlled blinded studies that evaluate the efficacy of lufenuron to prevent or alter the course of experimentally induced *M. canis* infections in cats.[32,33] Two oral doses (30 or 133 mg/kg) of lufenuron were evaluated; after 2 months of pretreatment, the kittens were challenged with infective *M. canis* spores. In this study, neither dose of lufenuron prevented infection nor altered the course of infection; however, the challenge was markedly larger than what would occur under field exposure.[33]

In a follow-up study, two groups of cats were pretreated with either oral or injectable lufenuron before exposure to a subclinically infected cat.[32] Cats received four doses of lufenuron at monthly intervals (100 to 133 mg/kg PO or 40 mg SQ) before exposure to the infected cat, and monthly treatments thereafter for an additional 5 months. In this study, lufenuron did not prevent infection in either treatment group. In addition, infections in the control and two treatment groups resolved at about the same time. What was noticed in this study was that

Table 32-4 | **General Recommendations for Topical Antifungal Therapy**

The most consistently effective antifungal topical agents are lime sulfur, enilconazole, and miconazole.
Twice-weekly application as a whole body rinse or shampoo (depending upon formulation) is recommended.
Topical therapy is best used in conjunction with a systemic antifungal drug.
If topical therapy is used as a sole therapy, the hair coat should be clipped and lime sulfur or enilconazole should be used.
Cats should not be allowed to remove the antifungal solutions by licking or grooming.

infections were established more slowly in the lufenuron-treated groups when compared with the control group. In a clinical field study involving 100 cats in two catteries with naturally occurring dermatophytosis, cats were divided randomly into two treatment groups.[15] Both groups were treated topically with enilconazole once weekly, but one group received griseofulvin (25 mg/kg PO q24h) and the other lufenuron (60 mg/kg). Although the investigators reported a decrease in fungal culture counts over 90 days and resolution of clinical signs, cures were not reported.[15] *At this time, we do not recommend lufenuron for the treatment or prevention of dermatophytosis.*

Fungal Vaccines

Without a doubt, intense interest continues in the development of a fungal vaccine for the prevention of dermatophytosis. Several studies have been conducted on the use of an experimental or commercial vaccine for the treatment and prevention of dermatophytosis.[37-42] At this time, no fungal vaccines are commercially available for use in cats; Fel-O-Vax MC-K (Fort Dodge Laboratories, Fort Dodge, Iowa) currently is unavailable. The following are key findings from the above-mentioned studies of feline vaccines:

- To date, fungal vaccines are not protective against challenge exposure in cats.
- Fungal vaccines have been associated with a temporary reduction in the clinical signs of feline dermatophytosis.
- To date, fungal vaccines are not effective as sole therapy in the treatment of feline dermatophytosis.

CONCLUSION

Current treatment strategy recommendations are summarized in Tables 32-2 through 32-5. These recommendations are based upon these authors' interpretations of the studies summarized in this chapter and may differ from those of other clinicians.

Table 32-5 | **Summary of Current Treatment Recommendations***

CLIPPING OF THE HAIR COAT
Clipping of the hair coat is always optimum but not always needed in every case.
Clipping of the hair coat is the most cost-effective method to decrease environmental contamination.
Clipping is recommended, especially in shorthaired cats with generalized lesions (less than five lesions) and all long-haired cats.
TOPICAL THERAPY OPTIONS
Lime sulfur or enilconazole are the only topical antifungal agents that can be used as sole therapy.
The most common reason for failure of sole topical therapy is inadequate thorough application of the solution; the face and ears often are overlooked or undertreated.
Topical therapy is best used as an *adjuvant* to systemic therapy.
Topical therapy should be used twice weekly.
Lime sulfur 8 ounces/gallon
Enilconazole
SYSTEMIC TREATMENT OPTIONS
Itraconazole
Daily dosing: Itraconazole 10 mg/kg PO q24h
Combined continuous/pulse therapy: Itraconazole 10 mg/kg PO q24h for 28 days, and then on an alternate week regimen (1 week off and 1 week on)
Short-term cycle therapy: Itraconazole 10 mg/kg PO q24h for 15 days, followed by fungal cultures 10 to 15 days post treatment. These cycles are repeated until the cats are cured.
Terbinafine
Daily dose: 30 to 40 mg/kg PO q24h
Terbinafine (30 to 40 mg/kg PO) may be substituted for itraconazole in continuous/pulse or cycle therapy.
Griseofulvin
Daily micro size 50 mg/kg PO q24h or divided q12h
Daily ultramicrosize 10 to 15 mg/kg PO q24h or divided q12h
ALTERNATIVE THERAPIES
Fungal vaccines are not effective as sole therapies or as prophylaxis against infection.
Lufenuron is not effective in the treatment and/or prevention of infection and should not be used in the treatment of feline dermatophytosis.

*Modified and adapted for publication in this chapter from Moriello KA: Treatment of dermatophytosis in dogs and cats: review of published studies. Vet Dermatol 15:99-107, 2004; Moriello KA: Feline dermatophytosis symposium parts 1-4. Vet Med 98:844-891, 2003.

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Chapter 33

CARDIOMYOPATHY—ESTABLISHING A DIAGNOSIS

Virginia Luis Fuentes

Myocardial disease is common in cats and can occur in several forms and different degrees of severity. Feline cardiomyopathy can be a diagnostic challenge for many reasons, from the occult nature of asymptomatic hypertrophic cardiomyopathy to the blurred boundaries between categories in end-stage myocardial disease. A diagnosis can be achieved only by combining skills in physical examination and diagnostic imaging with a sound understanding of myocardial structure and function across the spectrum of feline myocardial disease.

CLASSIFICATION OF FELINE CARDIOMYOPATHIES

The traditional classification in cats mirrored the human cardiomyopathy classification, with idiopathic categories of hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and restrictive cardiomyopathy (RCM).[1] Cats that did not fit these categories were described variously as intermediate, intergrade, or unclassified. Specific heart muscle diseases (for which the underlying cause was known) were classified separately. As new underlying causes continue to be discovered for cardiomyopathies previously considered "idiopathic," this old classification has been supplanted by a new one, based on the predominant pathophysiology.[2] This system retains the commonly recognized clinical entities of HCM, RCM, and DCM, even if a specific underlying etiology is recognized. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is included as a fourth category (see Chapter 35), and cardiomyopathies of unknown cause that do not fit into the four categories above are termed unclassified cardiomyopathy (UCM). Cats, too, are now classified according to this system.

ETIOLOGY

The role of taurine in the etiology of many cases of feline DCM was established clearly in the late 1980s.[3] The formulation of canned cat food at the time reduced the bioavailability of taurine, resulting in reduced plasma and myocardial levels of taurine and subsequent myocardial failure.[4] This form of DCM was reversible with taurine supplementation.[3] A change in the formulation of commercial cat food has meant that most current feline cases of DCM have normal plasma taurine levels and are considered to be idiopathic, as in other species.

Studies in human patients and transgenic mice have uncovered a genetic basis for many cardiomyopathies. It appears that mutations of sarcomeric proteins result frequently in HCM phenotypes, whereas cytoskeletal abnormalities are more likely to result in DCM-type phenotypes, although some overlap occurs.[5] Several mutations can cause either a DCM- or HCM-type phenotype, with an initial phase of left ventricular hypertrophy leading ultimately to overt systolic dysfunction and ventricular dilation.[6] The hypertrophy seen in HCM is believed to be an excessive growth response to dysfunction of contractile proteins on a molecular level. Whether genetic mutations are responsible for myocardial disease in cats is uncertain,[7] but familial forms of feline cardiomyopathy have been described and a genetic basis is suspected strongly in at least some cats.[8-11] The endomyocardial form of feline RCM may be associated with prior endomyocarditis.[12] Pathological processes such as myocarditis or infarction may occur in any of the cardiomyopathies, further altering the phenotype and making a diagnosis more difficult for the clinician.

TYPES OF CARDIOMYOPATHY

The most common form of cardiomyopathy is HCM, with RCM, DCM, and ARVC occurring much less frequently.[13,14] Cats with HCM sometimes are diagnosed while asymptomatic, after incidental detection of a murmur. Because some cats with myocardial disease show no abnormalities on physical examination, the true prevalence of asymptomatic feline HCM probably has been underestimated. It is less usual for the other forms of cardiomyopathy to be diagnosed before the onset of congestive heart failure or systemic thromboembolism. We lack long-term prospective data on the natural history of feline

myocardial disease, although long-term retrospective studies of HCM have been reported.[15,16]

Hypertrophic Cardiomyopathy

In addition to being the most common of feline myocardial diseases, HCM also is the form with the most varied presentation. It is characterized by left ventricular (LV) hypertrophy of unknown cause, so other conditions resulting in LV hypertrophy such as systemic hypertension, aortic stenosis, or hyperthyroidism should be excluded. The hypertrophy may be localized to all or part of the interventricular septum or free wall, or may occur throughout the whole ventricle, with the papillary muscles often markedly hypertrophied. The localized hypertrophy seen in the basal septum of many elderly cats usually is not classified as HCM. An irregular arrangement of the myocyte (myofiber disarray) is one of the hallmarks of human HCM and may be present in varying proportions of the myocardium.[17] Myocardial fibrosis is common, especially in areas with abnormal small intramural coronary arteries.[17] Myocardial infarction may occur, appearing as localized wall thinning with scarring, and myocarditis also has been noted.[18]

The pathophysiological effects of this hypertrophy range from minimal hemodynamic significance to severe diastolic dysfunction. Impaired ventricular relaxation and increased ventricular stiffness may limit ventricular filling, leading to increased atrial pressures and congestive heart failure (CHF). Dynamic left ventricular outflow tract obstruction (LVOTO) is common, in which the anterior mitral valve leaflet moves towards the LV outflow tract during ejection instead of coapting normally. This results in dynamic obstruction to ejection and may be intermittent or persistent. This finding has been associated with a worse prognosis in human patients,[19] although this has not been demonstrated in cats.[16]

Clinical Presentation

The classic presentation for HCM is a young male adult cat, but the signalment can be varied.[15] It may be seen in kittens and in cats more than 10 years of age.[20] Some breeds may be predisposed, such as Maine coons, Persians, and Cornish rexes. Some affected cats may evade diagnosis if asymptomatic, particularly if no abnormalities are present on physical examination. Even cats with congestive heart failure may not have a detectable murmur, gallop sound, or arrhythmia, although any of these findings may be present. The onset of clinical signs in cats with pulmonary edema may be sudden and severe, although owners do not always detect signs of respiratory distress reliably. Cats with moderate pleural effusions also may appear unremarkable to their owners. Systemic thromboembolism generally causes peracute clinical signs and may mimic a traumatic episode.

Dilated Cardiomyopathy

The classic features of DCM include systolic dysfunction and ventricular remodeling, resulting in dilation of all four chambers and a thin-walled and more spherical left ventricle than normal, with small papillary muscles.[21] If these morphometric features alone are used to define DCM, some overlap may occur with the end-stage forms of other myocardial diseases.

Clinical Presentation

Taurine-deficiency DCM is now restricted mostly to cats fed on dog food. The majority of cats with DCM are middle-aged or older. Cats with dilated cardiomyopathy are diagnosed rarely while asymptomatic and present generally with a combination of output failure and congestive signs. Hypotension, hypothermia, and bradycardia are the hallmark signs of output failure and may be present even in the absence of congestive signs. Pleural effusion is common when CHF is present. Thromboembolic disease also is common (see Chapter 37).

Restrictive Cardiomyopathy

The defining feature of RCM is increased ventricular stiffness with relatively normal left ventricular dimensions and systolic function. The decreased ventricular compliance impairs diastolic filling severely, which results in atrial dilation and increased atrial pressures. Two main forms are recognized: an endomyocardial form and a myocardial form.[13] The endomyocardial form is associated with severe endomyocardial fibrosis and scarring, which may result in obliteration of the mid to distal portion of the left ventricular cavity with fibrous tissue. Inflammatory infiltrates indicative of endomyocarditis may be found and may represent an initiating process.[12] The myocardial form is associated with more diffuse myocardial fibrosis, which may be less obvious than in the endomyocardial form. In both types, atrial dilation may be substantial. Any LV hypertrophy or systolic dysfunction tends to be mild.

Clinical Presentation

Affected cats generally are older and diagnosed rarely while asymptomatic. Biventricular congestive failure usually is present, and both arrhythmias and thromboembolic disease are common.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is characterized by fatty or fibrofatty infiltration of the right ventricle, resulting in marked right heart enlargement.[22] Myocarditis also may be present. Affected cats may be asymptomatic or may have a history of syncope in association with arrhythmias. Right-sided CHF is seen in other cats. The natural history is less well defined than in the other forms of feline myocardial disease, because ARVC has been recognized only recently in cats. Previously, affected cats may have been diagnosed mistakenly with tricuspid dysplasia (see Chapter 35).

APPROACH TO DIAGNOSIS OF MYOCARDIAL DISEASE

Diagnosis depends first on determining that cardiac disease is present and then on distinguishing myocardial disease from other types of cardiac disease (Table 33-1). Finally, the specific form of myocardial disease should be determined.

If classification of the type of myocardial disease after imaging studies is still not possible, then at a minimum, an assessment should be made of the type of functional disturbance present. This may include whether an indication exists

Table 33-1 | **Differential Diagnosis of Myocardial Disease According to Presentation**

PRESENTATION	POSSIBLE MYOCARDIAL DISEASE	OTHER DIFFERENTIAL DIAGNOSES
Asymptomatic cat with murmur	HCM ARVC	Functional murmur (anemia, high cardiac output, aortic dilation) Hyperthyroidism Systemic hypertension Congenital heart disease
Dyspneic cat without murmur	HCM and CHF DCM and CHF RCM and CHF ARVC and CHF	Pleural effusions Noncardiogenic pulmonary edema Intrapulmonary hemorrhage Asthma Heartworm disease Thromboembolism Mediastinal masses Pulmonary neoplasia, etc.
Dyspneic cat with murmur	HCM and CHF DCM and CHF RCM and CHF ARVC and CHF	Congenital heart disease Hyperthyroidism and CHF Anemia and CHF

of increased filling pressures (e.g., atrial dilation) and whether systolic function is normal.

History

If a murmur or gallop sound is detected in an asymptomatic cat presented for a routine health check, HCM is more likely than RCM or DCM, because the latter often are symptomatic at the time of presentation. Murmurs are a common finding in apparently healthy cats.[23] Cats with CHF usually present with respiratory distress, but if the owner has not detected this, vague signs may be reported, such as hiding, lethargy, inappetence, or even vomiting. Coughing is not seen typically with cardiac disease in cats. Cats with severe cardiac output failure may present with profound weakness. Cats with systemic thromboembolism usually present with acute onset pain and limb paresis, which may be mistaken for a traumatic episode by the owner. The hindlimbs are affected most commonly, but a single forelimb may be affected in some cats. With thromboembolism elsewhere, the signs may be more confusing, depending on the site (see Chapter 37).

Physical Examination

The absence of a murmur can mislead the unwitting clinician, and a high index of suspicion for cardiac disease should be maintained in any cat presenting with respiratory distress. Conversely, not all cats with a heart murmur have significant structural heart disease, particularly in high cardiac output states such as anemia or hyperthyroidism. Dynamic right ventricular outflow tract obstruction may result in a murmur in otherwise normal cats.[24] The loudest murmurs typically are found with HCM (although some HCM cats have no murmurs). Intermittent murmurs (murmurs that vary in intensity with excitement) are suggestive of either HCM with LVOTO, or functional murmurs. Cats with DCM and RCM tend to have very soft holosystolic murmurs over the left or right sternal border (or may not have an audible murmur). Arrhythmias may occur with any of the cardiomyopathies. A gallop sound can be a helpful finding, because this is a reasonably reliable sign of myocardial disease (although the clinician should note that in very elderly cats, a gallop sound may be associated with an age-related deterioration in diastolic function without significant structural heart disease).

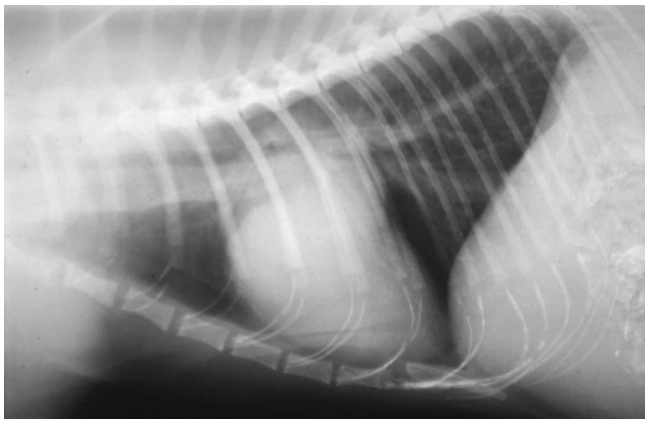
For cats with respiratory distress, observation of the respiratory pattern is very important. Pulmonary edema and pleural effusion can result in an increased respiratory rate with inspiratory and expiratory effort, and no audible airway noise. Crackles may be heard with pulmonary edema, and breath sounds are absent ventrally with pleural effusions. Most cats resent thoracic percussion. In HCM (and hyperthyroidism) the apical impulse may be especially prominent. Jugular distension may be evident with right heart failure (or some noncardiac pleural effusions). Femoral pulses may be weak in any of the cardiomyopathies, or absent with aortic thromboembolism. Ascites is far less common than pleural effusion in CHF as a result of cardiomyopathy, although ARVC sometimes results in ascites. Retinal changes may be seen in taurine-deficient cats, and in systemic hypertension.

Diagnostic Imaging

Confirmation of a diagnosis of myocardial disease usually is impossible without echocardiography, and thoracic radiographs are still the most practical means for confirming CHF.

Radiography

Asymptomatic HCM cats may have minimal changes on survey radiographs, especially if left atrial size is normal. Many cats with HCM have an elongated cardiac silhouette, although apparently normal films also can be seen in cats with mild HCM or cats with functional murmurs. Radiography cannot differentiate between the different forms of cardiomyopathy (Figures 33-1 and 33-2). Cardiomegaly and biatrial enlargement may be seen with HCM, RCM, and DCM. A globoid silhouette of pericardial effusion may be seen in any advanced cardiomyopathy. Pulmonary infiltrates can be very patchy with cardiogenic pulmonary edema, and alveolar infiltrates at times may appear almost granular (Figure 33-3). Pulmonary vessels (both arteries and veins) may be wide and tortuous, in contrast to heartworm disease, in which only the arteries are abnormal.



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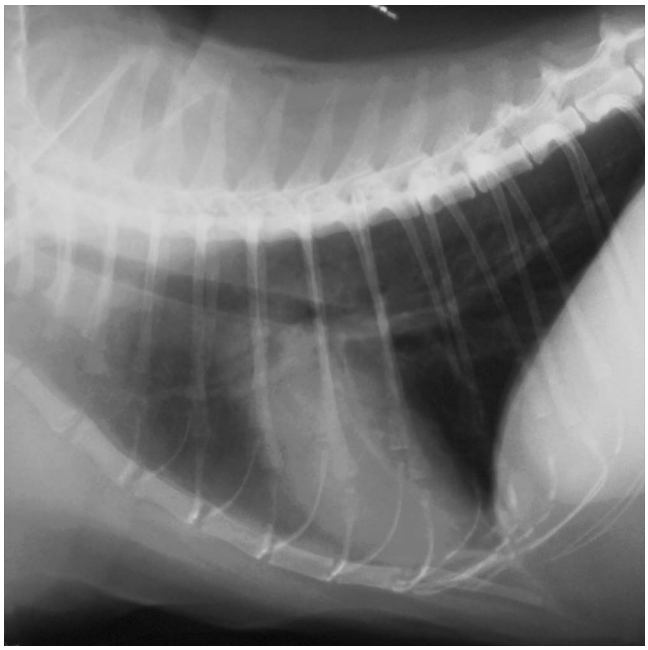

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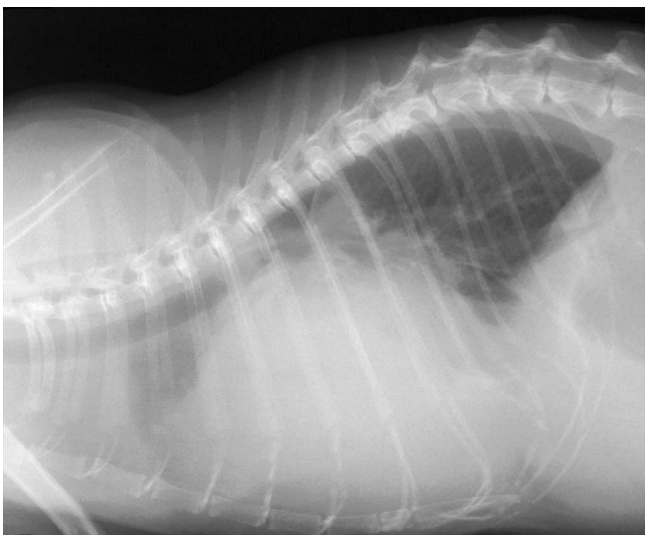
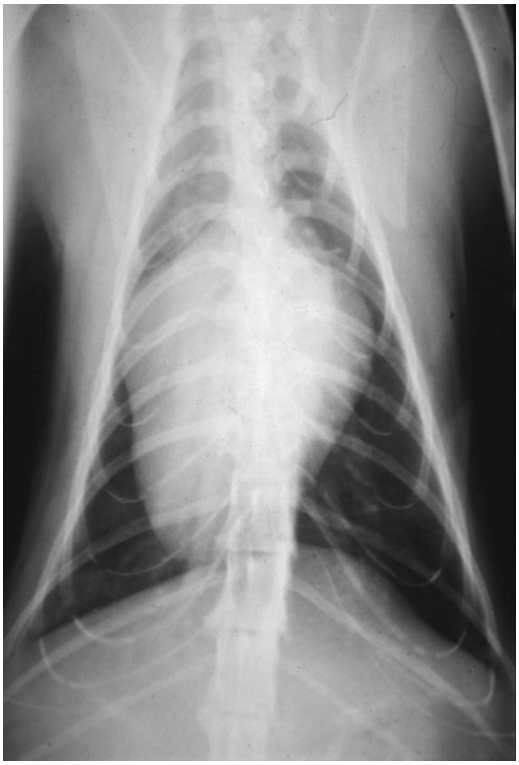


C

Figure 33-1. Lateral radiographs of three cats with myocardial disease. **A,** Cat with HCM and marked left atrial enlargement. **B,** Asymptomatic cat with HCM showing a typically elongated cardiac silhouette. **C,** Cat with RCM with pericardial and pleural fluid associated with congestive heart failure.



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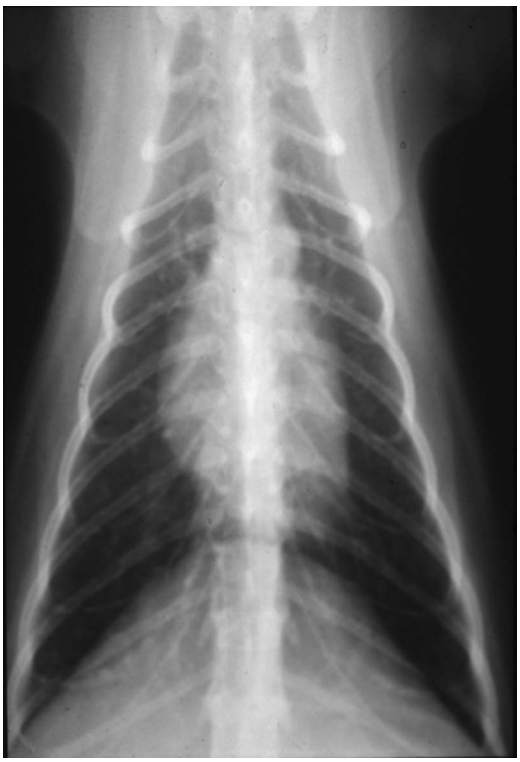
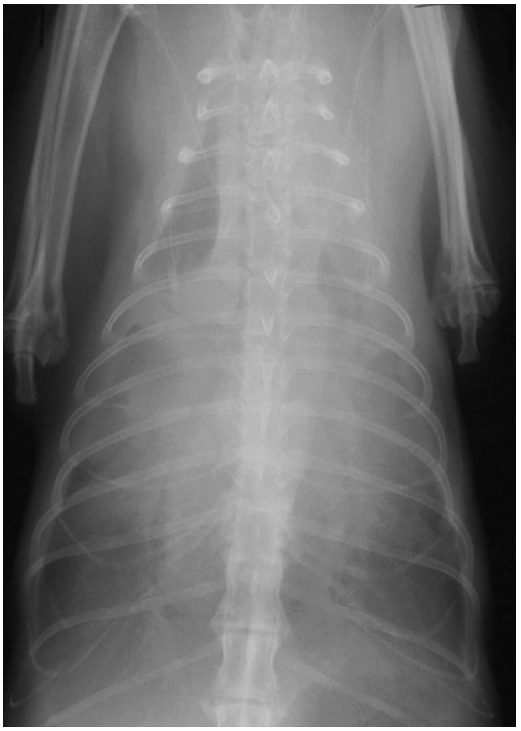
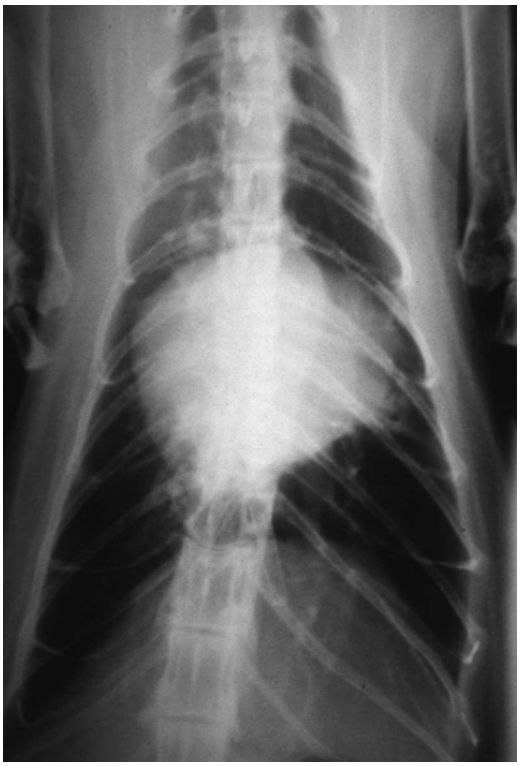


B

Figure 33-2. Dorsoventral thoracic radiographs of cats with myocardial disease. **A,** Same cat as in Figure 33-1, *A*. The apex commonly is shifted to the right in HCM. **B,** Cat with HCM (this is the same cat as in Figure 33-1, *B*).

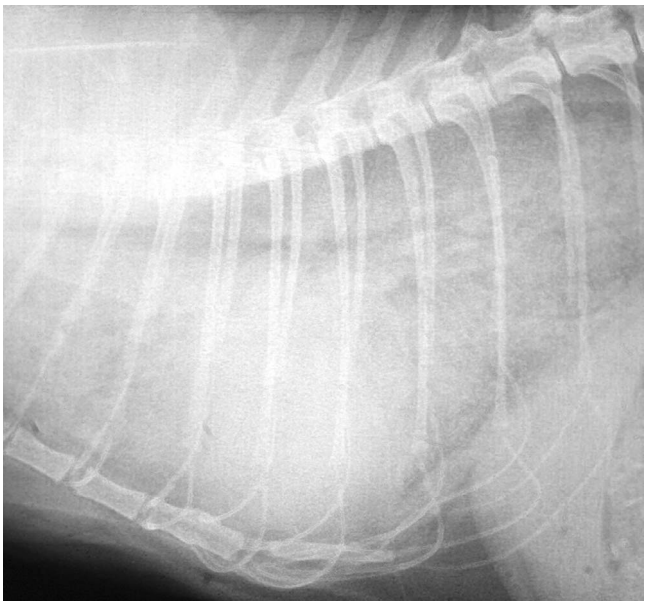


C



D

Figure 33-2.—cont'd. C, Cat with RCM (see Figure 33-1, *C*). **D,** Cat with RCM, showing severe biatrial enlargement.



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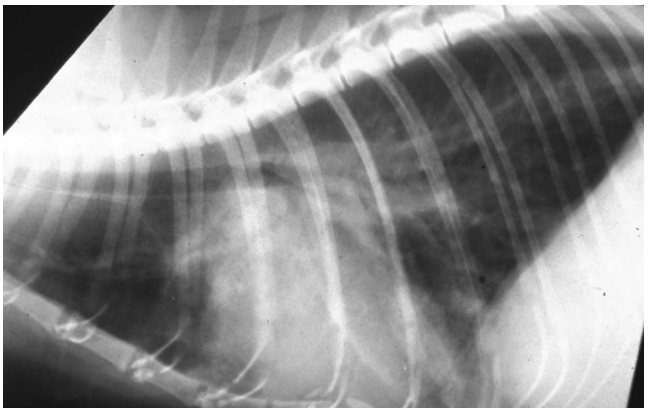

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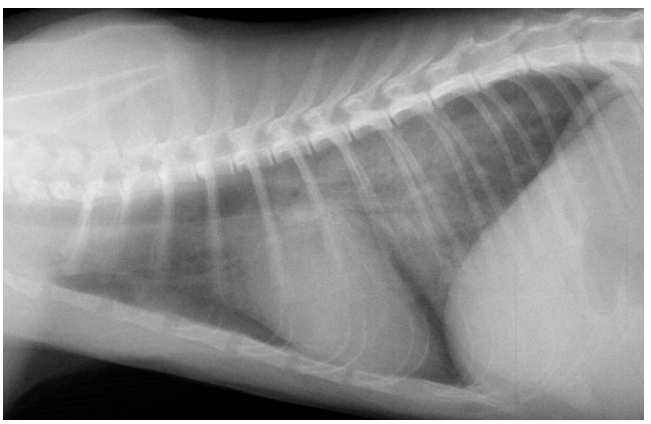


C

Figure 33-3. Cats with cardiomyopathy and pulmonary edema, ranging from severe generalized alveolar edema creating an almost nodular pattern **(A)** to patchy infiltrates and tortuous pulmonary vessels **(B)** or more hazy infiltrates **(C).**

Echocardiography

Echocardiography has become an essential tool for the diagnosis of feline myocardial disease. Both the structural and functional changes that occur with myocardial disease can be demonstrated well with a combination of two-dimensional echocardiography (2DE) and Doppler echocardiography (DE). Unfortunately, a fairly long and steep learning curve exists with feline echocardiography.

M-mode echocardiography can be useful for demonstrating increased LV diameter and reduced systolic function (often assessed using the LV fractional shortening) and for identifying systolic anterior motion of the mitral valve in HCM. Left atrial (LA) size is a very important measurement, because LA dilation suggests increased filling pressures. M-mode can be used to assess LA size using the LA:aortic ratio (generally around 1.0). However, a number of limitations exist with M-mode in assessing feline cardiomyopathy (Figure 33-4). In mild HCM, focal hypertrophy may be missed if the cursor does not pass through the affected area. In severe HCM, it can be difficult to avoid crossing through the papillary muscles.

Much more information can be obtained about morphology using 2DE. DE provides further refinement in the assessment of LVOTO and right ventricular outflow tract gradients, atrioventricular valve insufficiency, and diastolic function. Identification of the source of a murmur without DE can be difficult, but most of the diagnostic information still can be obtained by 2DE.

ECHOCARDIOGRAPHIC CHANGES IN HCM. Most clinicians consider the left ventricle to be hypertrophied if the septal or free-wall thickness measures 6 mm or greater in diastole.[25] The site of LV hypertrophy in HCM may not be imaged in all planes, so multiple 2DE views should be evaluated, measuring the end-diastolic wall thickness directly from the 2DE image (Figure 33-5).[25-27] LA size may indicate the degree of hemodynamic compromise, with LA size being greater in HCM cats dying with congestive failure than in HCM survivors in one study.[25] Systolic function usually is normal to hyperdynamic, and LV diameter usually is normal to reduced. Demonstration of systolic anterior motion of the mitral valve can indicate the cause of a systolic murmur in cats with HCM and LVOTO

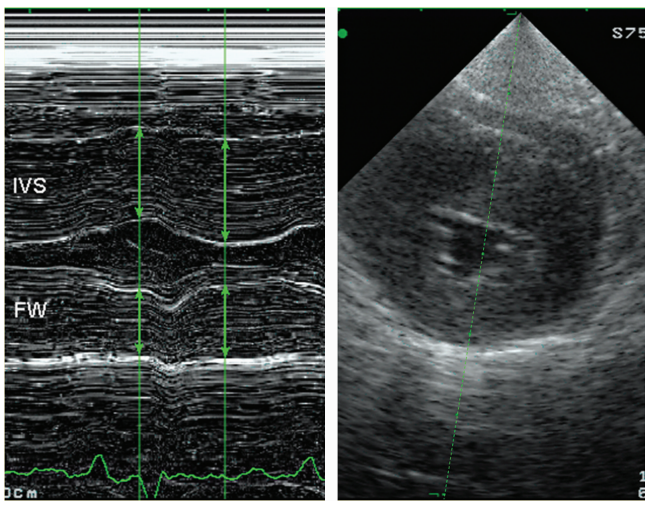
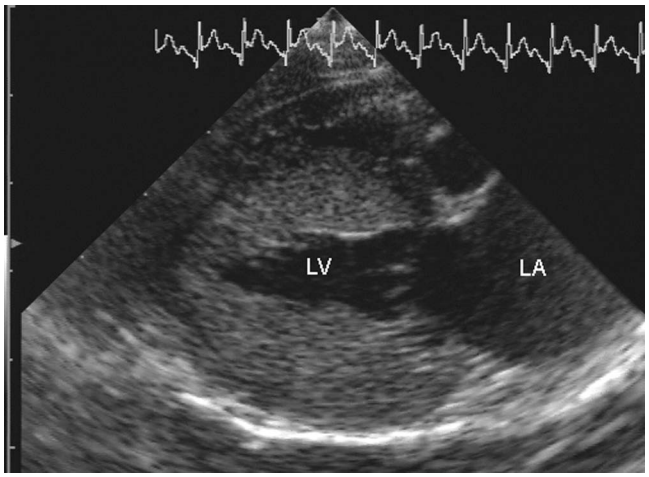


Figure 33-4. M-mode echocardiography only assesses wall thickness in one plane, and it can be difficult to avoid the papillary muscles.



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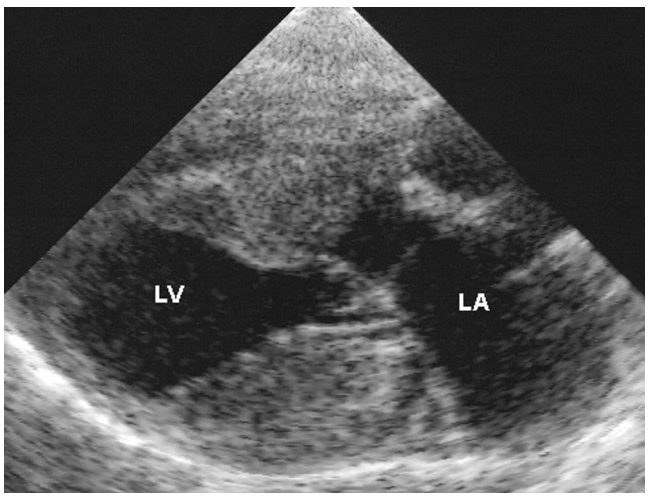

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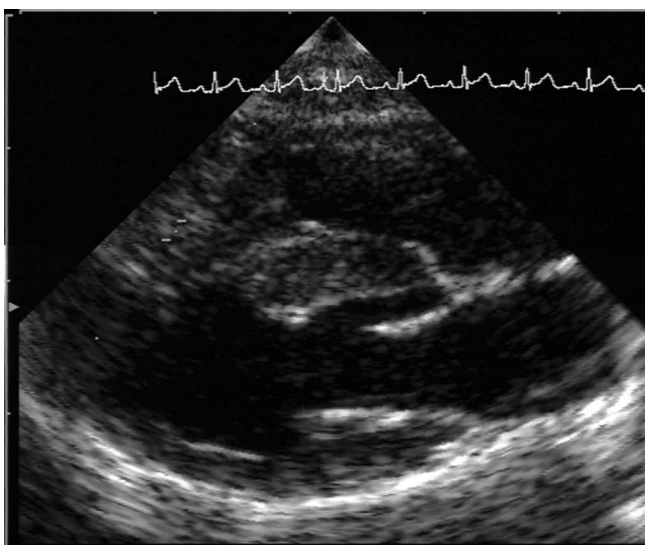
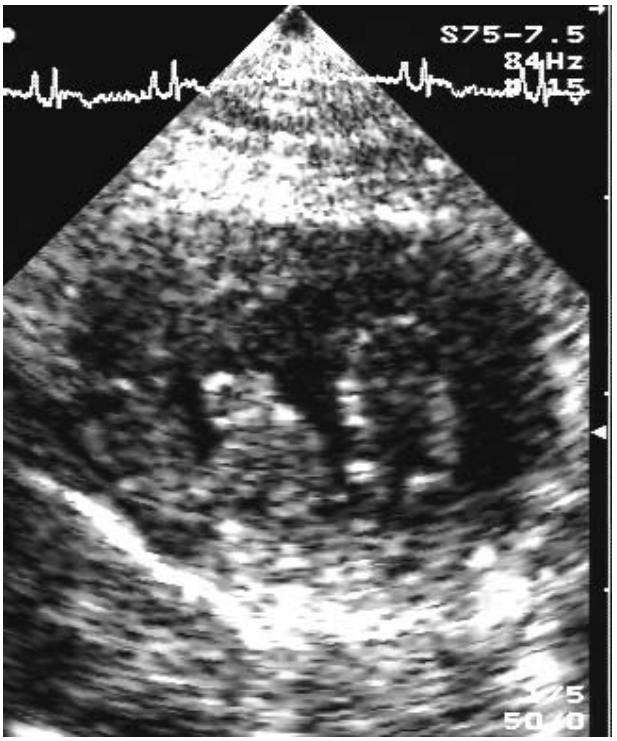


C

Figure 33-5. 2DE views of HCM, showing a range of severity. **A,** Severe generalized hypertrophy with left atrial enlargement. **B,** Hypertrophy in the basal portions of the septum and free wall, with sparing of the apex. **C,** Hypertrophy localized to the mid-septum, with hyperechogenicity of the endocardium at the same site.

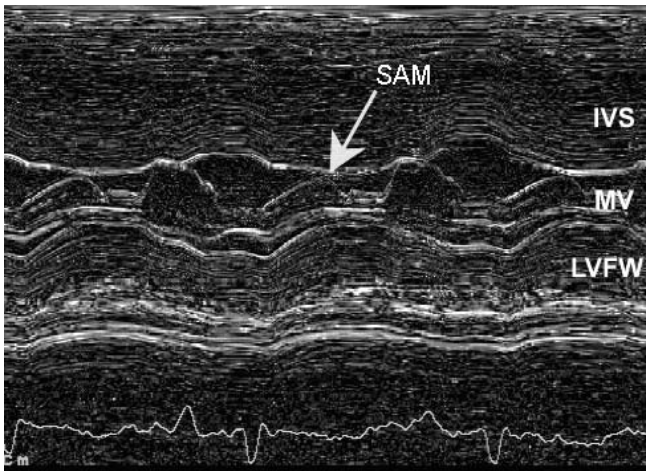


D

Figure 33-5.—cont'd. D, Short-axis view of the left ventricle, showing papillary muscle hypertrophy.

(Figure 33-6). Subaortic stenosis should be ruled out as a cause of the LV hypertrophy and not confused with small hyperechoic "kissing lesions" of the septum, in which mitral-septal contact occurs in LVOTO. Doppler echocardiography can be used to indicate the magnitude of the pressure gradient across the LV outflow tract in such cases, in addition to demonstrating the degree of associated mitral regurgitation. Diastolic function can be assessed comprehensively using a combination of mitral inflow velocity patterns, pulmonary venous flow velocities, Doppler tissue imaging, and color M-mode LV flow propagation velocities. Restrictive filling patterns are seen typically in cats with severe CHF, whereas delayed relaxation patterns are more common in asymptomatic cats.

ECHOCARDIOGRAPHIC CHANGES IN RCM. The endomyocardial form of RCM is recognized easily with 2DE, although M-mode images can be confusing. The endomyocardial scarring appears as thick hyperechoic bands crossing the LV, and severe biatrial enlargement usually is present. Some wall segments may be mildly hypertrophied, and systolic function usually is subjectively normal or only slightly reduced. The myocardial form may be more challenging, because the LV may appear relatively normal but with a markedly dilated LA (Figure 33-7). Atrial systolic function usually is poor, even in sinus rhythm. Pericardial effusion may be present as a result of right-sided heart failure. The severe ventricular stiffness and high atrial pressures associated with both forms result in a characteristic "restrictive" diastolic filling pattern, in which most of



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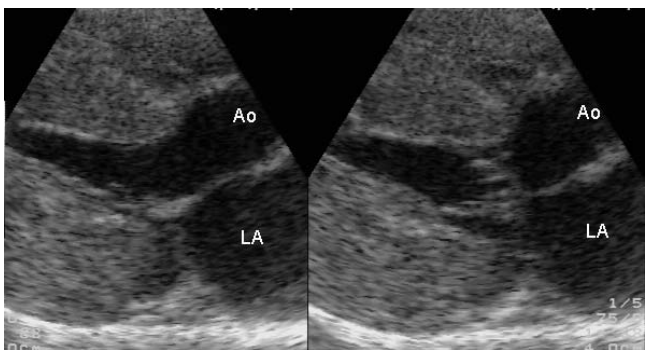

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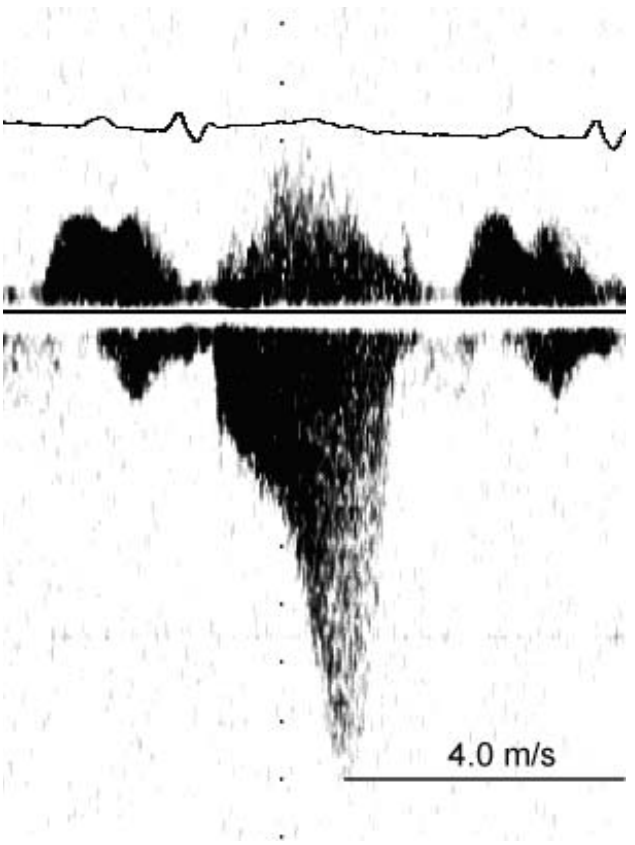
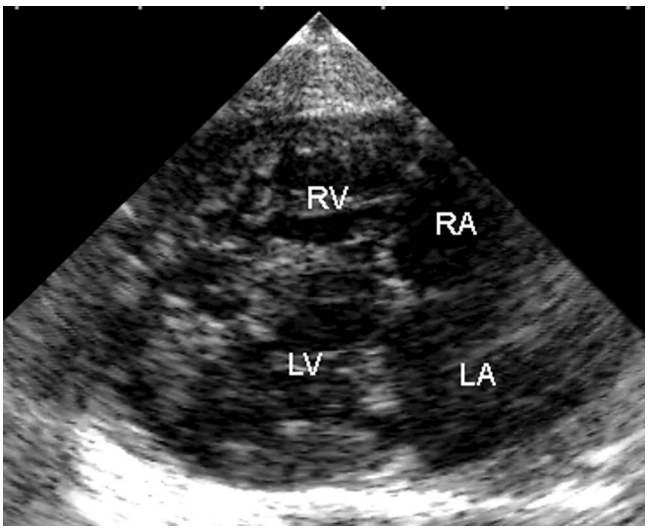


C

Figure 33-6. Systolic anterior motion of the mitral valve (SAM), which frequently is responsible for dynamic left ventricular outflow tract obstruction (LVOTO). **A,** The anterior mitral leaflet is moving towards the septum in systole *(white arrow)*. **B,** The same movement of the anterior mitral valve leaflet in late systole in a 2DE long-axis view. **C,** A spectral Doppler recording of increased blood flow velocities in the left ventricular outflow tract (normally less than 2 m/s). Note that the increased velocity occurs in late systole, resulting in a concave profile ("dagger" shape) to the spectral waveform.



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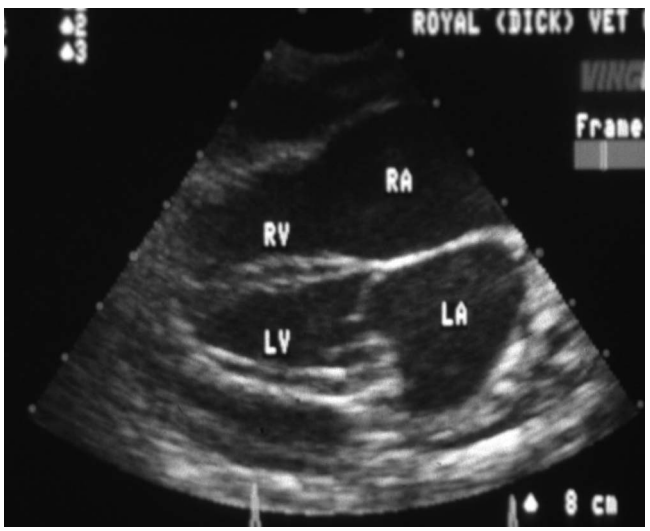

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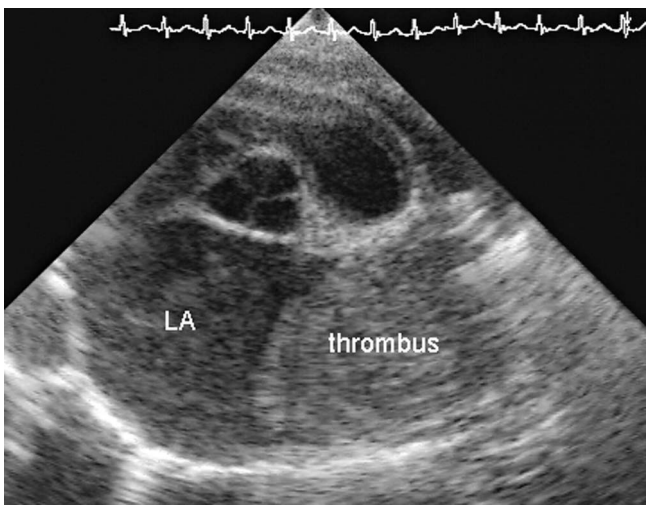


C

Figure 33-7. Restrictive cardiomyopathy. **A,** The endomyocardial form of RCM, with abnormal bands crossing the left ventricle. **B,** Biatrial dilation but normal LV dimensions, consistent with the myocardial form of RCM. **C,** Large thrombus in the left auricle.

the filling of the LV occurs rapidly at the beginning of diastole, but then stops after abrupt deceleration because of poor LV compliance (Figure 33-8). This pattern also can be seen in HCM or DCM but is seen virtually always with RCM.

ECHOCARDIOGRAPHIC CHANGES IN DCM. The dilation and increased sphericity of the LV are evident on 2DE, and the reduced systolic function can be assessed by M-mode (fractional shortening less than 30 per cent, with an LV end-systolic diameter greater than 12 mm). All four chambers may be dilated, or only the left heart (Figure 33-9). Hypokinesis of the free wall or septum is seen occasionally; these cats might represent an end-stage of HCM with infarction rather than being "true" DCM cats. Pericardial effusions often are present. Small central jets of mitral regurgitation (and tricuspid regurgitation) are seen frequently with color flow Doppler echocardiography.

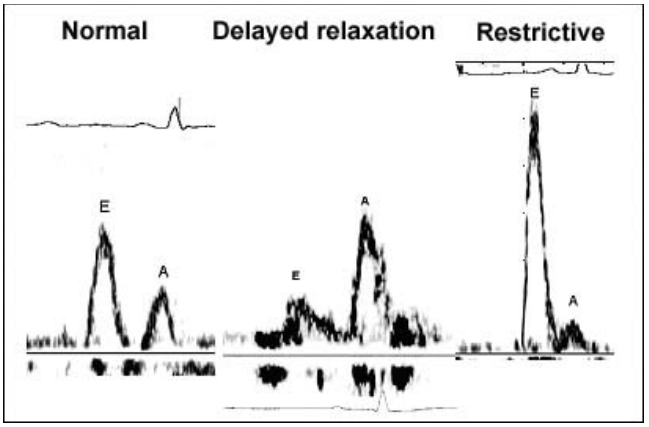
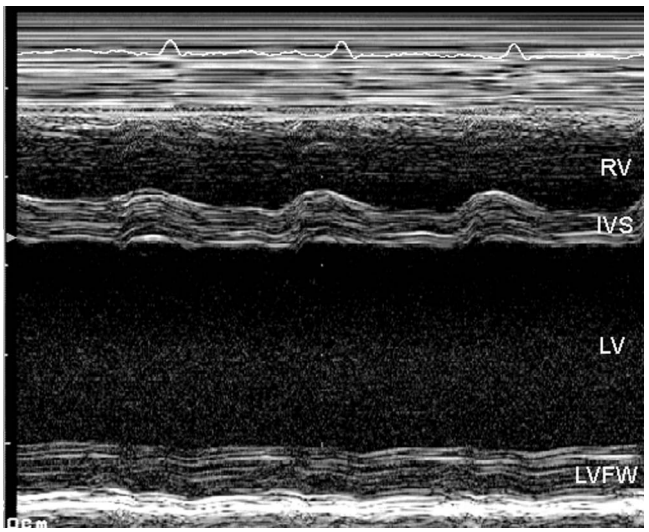
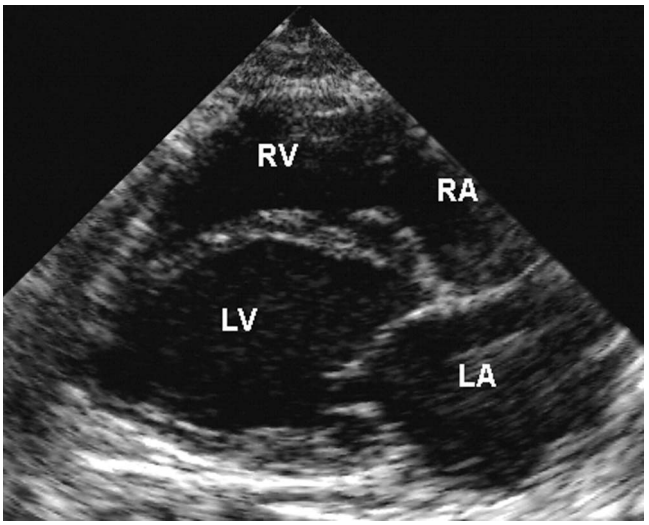


Figure 33-8. Spectral Doppler recordings of transmitral flow from three different cats, showing a normal distribution of filling through diastole; a delayed relaxation pattern in which the filling occurs predominantly late in diastole; and a restrictive pattern, in which virtually all filling occurs at the beginning of diastole.



A

Figure 33-9. Dilated cardiomyopathy. **A,** M-mode recording of the left ventricle, showing extremely poor wall motion associated with severe systolic dysfunction.



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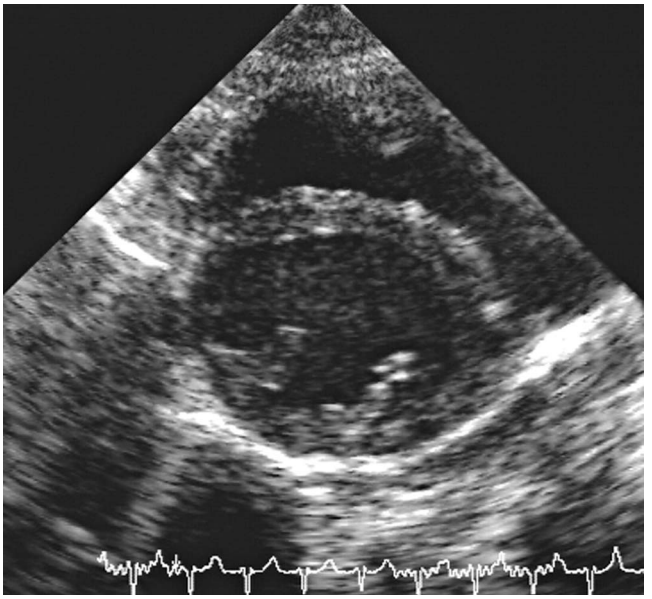

C

Figure 33-9.—cont'd. B and **C,** Dilation of all four chambers with thinning of the LV wall.

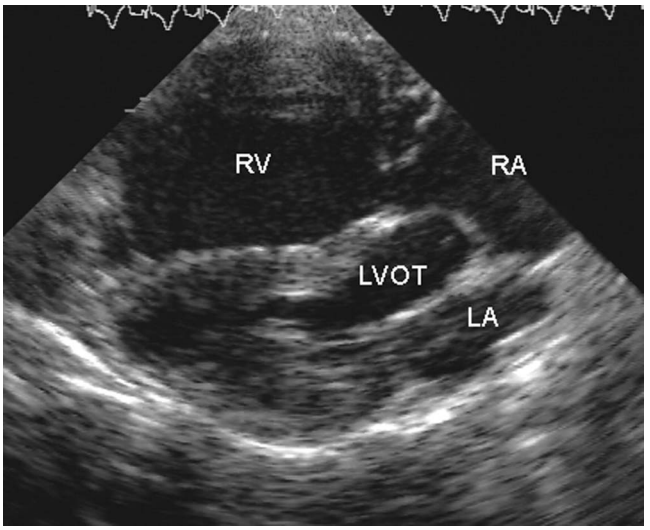

Figure 33-10. Arrhythmogenic right ventricular cardiomyopathy (ARVC) showing massive dilation of the right ventricle.

ECHOCARDIOGRAPHIC CHANGES IN ARVC. The typical findings with ARVC are severe right ventricular and right atrial dilation (Figure 33-10, see also Figure 35-2). It can be difficult to recognize the RV wall thinning, and the tricuspid valve may be considered abnormal mistakenly, because the dilation distorts the normal architecture. Nevertheless, the presence of an abnormal trabecular pattern near the apex of the RV can give some clues. Tricuspid regurgitation usually is present and is often substantial (but of normal velocity).

Other Diagnostic Tests

ELECTROCARDIOGRAPHY. ECG abnormalities may be seen in all forms of cardiomyopathy, and an abnormal ECG can be helpful when considering whether to undertake expensive diagnostic imaging.[13] A left anterior fascicular block pattern is associated particularly with HCM or hyperthyroidism and may be found in asymptomatic and symptomatic HCM cats. Wide P waves may be seen with any cardiomyopathy when left atrial enlargement occurs, and increased QRS voltages also may be seen with any form. Conversely, small voltages may be present whenever pleural or pericardial effusions occur. A variety of arrhythmias may be seen with any myocardial disease (Figure 33-11). Atrial arrhythmias may occur whenever severe atrial enlargement exists, and ventricular arrhythmias may be seen in all forms. First-degree atrioventricular block may be particularly common with DCM.

LABORATORY TESTS. Troponin-I levels may prove useful in the future as a possible screening test when deciding whether to undertake further tests such as echocardiography (levels may be elevated in HCM).[28,29] Systemic arterial blood pressure must be measured in cases of LV hypertrophy to rule out systemic hypertension as a cause. Thyroxine levels also should be measured in any middle-aged or older cat. In cats with DCM, plasma taurine levels should still be measured. Necropsy is the ultimate way to establish a diagnosis, but obviously is not helpful in management of the individual patient.

SUMMARY

Myocardial disease is common in cats but is not always easy to diagnose. A careful history and physical examination can lead to a strong suspicion of myocardial disease, but further imaging studies are necessary to confirm the type of myocardial disease and to stage the severity. Not all cats will fit neatly into the categories mentioned above, and most attention should be concentrated on changes indicative of increased filling pressures (such as increased left atrial size). Abnormal findings on electrocardiography or radiography may be helpful when deciding on the need for further diagnostic imaging, and blood

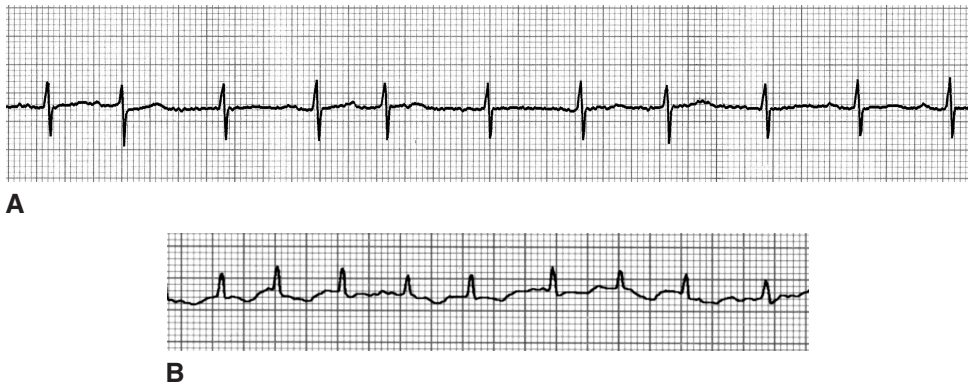

Figure 33-11. Because P waves frequently are small in cats, it can be very difficult to distinguish frequent atrial premature complexes (APCs) from atrial fibrillation. **A,** APCs (second and fifth complexes) with P waves only visible in the last two complexes. **B,** Atrial fibrillation, with random variation in R-R intervals and no visible P waves.

tests such as troponin-I levels may prove useful in the future as an initial screening test for significant myocardial disease.

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Chapter 34

Cardiomyopathy—Therapeutic Decisions

Sonya G. Gordon

Cardiomyopathies are common in cats. They occur in several forms with differing degrees of severity. Degrees of severity can be divided clinically into three groups.

Group 1 comprises symptomatic cats showing clinical signs of heart disease. Clinical signs of heart disease suggestive of congestive heart failure (CHF) may include dyspnea, tachypnea, and cough (rarely). Signs associated with arrhythmias or forward heart failure may include weakness, collapse, or syncope. Signs associated with arterial thromboembolism (ATE) may include lameness, paresis, or paralysis (see Chapters 37 and 58). Symptomatic cats then can be divided further into those patients with acute severe clinical signs requiring emergency therapy and those with chronic clinical signs requiring long-term management (Figure 34-1).

Group 2 is made up of asymptomatic (occult) cats with echocardiographic evidence of substantial morphological or functional cardiac disease or electrocardiographic (ECG) evidence of an important arrhythmia. Substantial cardiac disease is assumed if any of the following are identified: morphological cardiac changes suggestive of increased filling pressure (left atrial enlargement [LAE], M-mode left atrial:aortic ratio [La:Ao] greater than 2), unequivocal ventricular concentric hypertrophy (left ventricular posterior/free wall in diastole [LVPWd] greater than 8 mm or intraventricular septum in diastole [IVSd] greater than 10 mm), myocardial infarction, moderate to severe dynamic left ventricular outflow tract obstruction (LVOTO) (Doppler estimated gradient greater than 50 mm Hg), clinically important arrhythmias, systolic dysfunction, intracardiac thrombus or spontaneous echocardiographic contrast or "smoke" (see Chapters 37 and 58 and Figure 34-2).

Group 3 comprises asymptomatic cats with no cardiac changes suggestive of increased filling pressures (normal left atrial size), mild ventricular concentric hypertrophy, mild dynamic LVOTO, or mild arrhythmias (occasional premature beats).

Groups 2 and 3 usually are recognized during wellness evaluations by the identification of a murmur, gallop rhythm, or arrhythmia. Alternatively, they are discovered during the evaluation of other clinical abnormalities. Although not all asymptomatic cats with a murmur, gallop rhythm, or arrhythmia have clinically important underlying cardiac disease, an echocardiogram (and ECG if an arrhythmia is suspected) should be recommended. One recent report suggested that as many as 86 per cent of clinically asymptomatic cats with a murmur have echocardiographic evidence of heart disease.[1] Evaluation of biomarkers such as tumor necrosis factor-α and troponin-I someday may facilitate diagnosis, clinical staging, prognosis, and response to therapy.[2-5]

Recommendations for therapy of asymptomatic cats with heart disease (groups 2 and 3) pose a clinical challenge. Minimal therapeutic efficacy data are available in the veterinary literature. Most therapeutic recommendations are based on short-term prospective studies, retrospective-descriptive studies, extrapolation from other species, and clinical experience. Additionally, all recommendations must take into consideration individual client and patient preferences. Many clients are unable or unwilling to treat with more than two daily medications, which has important ramifications on standard of care. With rare exceptions, we are restricted currently to oral cardiac medications for chronic therapy. Although most oral cardiac medications are in tablet form, the tablet strengths often are too high to allow accurate dosing using pill splitters. Many doses therefore are reported on a per-cat basis and represent an approximate dose in many situations. On the other hand, many commonly used cardiac medications are available as a suspension or chewable formulation through compounding pharmacies (Table 34-1). Suspensions and chewable formulations may be better tolerated by some cats and clients and offer the advantage of more accurate dosing. To date, no transdermal preparations of cardioactive drugs have demonstrated adequate absorption (see Chapter 18). Therefore medications prescribed for life-threatening conditions such as CHF should not be offered in this formulation.[6]

In the case of many asymptomatic cats, particularly those in group 3, the most appropriate recommendation for most clients and patients may be surveillance and reevaluation. Although hypertrophic cardiomyopathy (HCM) is the most common form of cardiomyopathy and is recognized in purebreds and domestic short-hairs and long-hairs, surveillance and

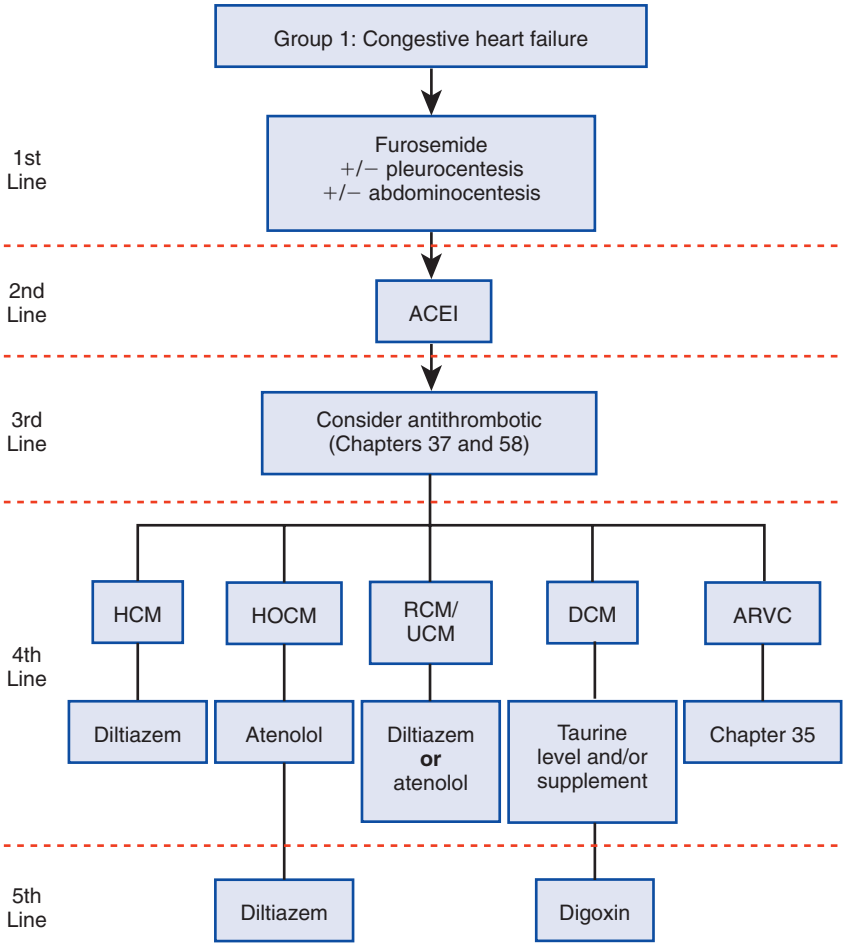

Figure 34-1. Diagnostic and treatment algorithm for cats with congestive heart failure.

Table 34-1 | **Commonly Used Medications for the Treatment of Feline Cardiac Disease**

DRUG	CLASS	DOSE (PER CAT)	DOSE (MG/KG)
Enalapril* or benazepril*	ACEI	PO: 1–2.5 mg q12–24h	PO: 0.2–0.7 mg/kg q12–24h
1. Diltiazem	Calcium-channel blocker	1. PO: 7.5 mg q8h	
2. Cardizem CD			2. PO: 10 mg/kg q24h
3. Dilacor XR		3. PO: 30–60 mg q12–24h	
Atenolol*	Beta-blocker	PO: 3.125–12.5 mg q12–24h	PO: 1.1–2.5 mg/kg q12–24h
Atenolol-low dose*	Beta-blocker	PO: 1–3.125 mg q24h Up titrate if well tolerated	
Furosemide*	Diuretic	PO: 3.125–12.5 mg q12–48h	PO: 1–2 mg/kg q12–48h IV/IM/SQ: 0.5–2 mg/kg prn
Hydrochlorothiazide*	Diuretic	PO: 6.25–12.5 mg q12h	PO: 2–4 mg/kg q12h
Spironolactone*	Aldosterone antagonist	PO: 6.25 mg q12h	PO: 1–2 mg/kg q12h
Digoxin	Cardiac glycoside	PO: 0.31 mg q24–48h	
Aspirin	NSAID	PO: 81mg q3days	PO: 25 mg/kg q3days
Sotalol*	Antiarrhythmic beta-blocker	PO: 10 mg q12h	
Nitroglycerine paste	Vasodilator	Topical: $\frac{1}{8}$–$\frac{1}{4}$ inch q6–8h	
Low-molecular-weight heparin	Antithrombotic		SQ: 100 IU/kg q12–24h
Butorphanol	Anxiolytic		IV/IM/SQ: 0.2 mg/kg prn
Taurine	Amino acid	PO: 250–500 mg q12h	

*Available as a suspension from a formulation pharmacy.

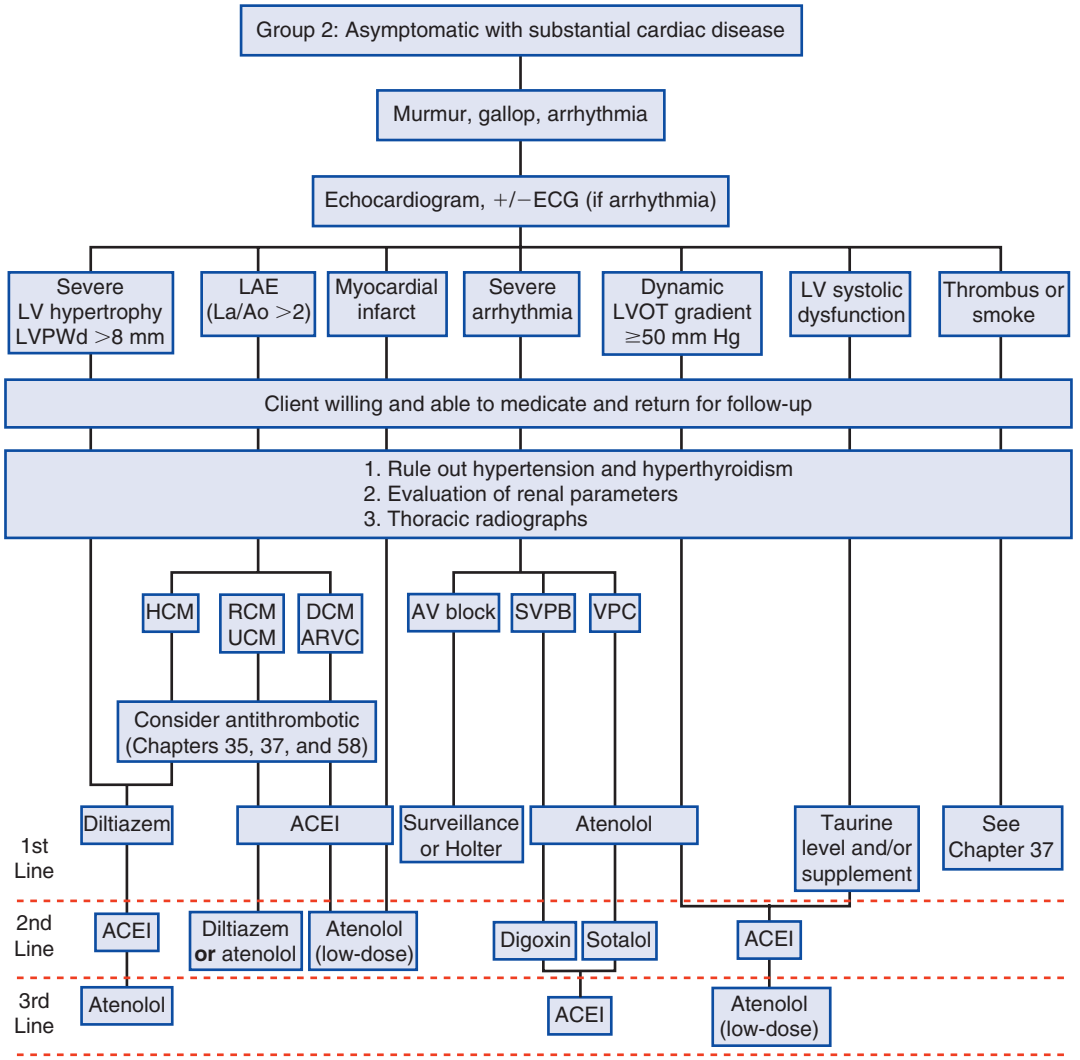

Figure 34-2. Diagnostic and treatment algorithm for asymptomatic cats with substantial cardiac disease.

reevaluation may be particularly important in young male patients with equivocal diagnostic findings and a high index of suspicion based on signalment; for example, male purebred cats with a reportedly high incidence of HCM such as Persians, Himalayans, Birmans, Ragdolls, Maine coons, and American short-hairs.[7-10] Additionally, severe HCM has been described in cats as young as 2 months of age, which makes the recommendation of an echocardiogram independent of age and murmur grade[9] (Figure 34-3).

Decisions regarding therapy can be approached with use of the groups outlined above. Emergency therapeutic recommendations for patients with severe clinical signs of CHF or ATE are independent of the underlying form of cardiomyopathy. The management of chronic heart failure, acute heart failure after stabilization (Group 1, see Figure 34-1), and asymptomatic clinically important heart disease (group 2, see Figure 34-2) is influenced greatly by echocardiographic characterization of underlying cardiac abnormalities (e.g., LAE, infarct) and ultimately definitive diagnosis.

The goal of therapy in symptomatic patients is to relieve clinical signs and prolong survival. The lofty goal in asymptomatic patients is to prolong the asymptomatic phase of disease and subsequently prolong survival. Identification and treatment of asymptomatic cardiomyopathies presuppose all cardiomyopathies progress, resulting in the development of clinical signs or death. This is not necessarily a priori. Some cats may have a mild phenotype that fails to progress, making client education regarding development of clinical signs and formulation of a surveillance plan to assess disease progression two important aspects of therapy. There currently are no prospective data on the natural history of any form of asymptomatic cardiomyopathy, and no medication has been shown to delay the progression of asymptomatic HCM based on surrogate endpoints such as reductions in left atrial size or left ventricular hypertrophy.[11] Therefore, all current recommendations are based on scientific rationale and proof of safety and reconciled ultimately with patient tolerance, which contributes to client compliance.

All feline cardiomyopathies share a similar pathophysiology: they all have the potential to progress, resulting in the recurrence or development of clinical signs consistent with CHF and ATE (see Chapter 37). Once CHF has developed, ther-

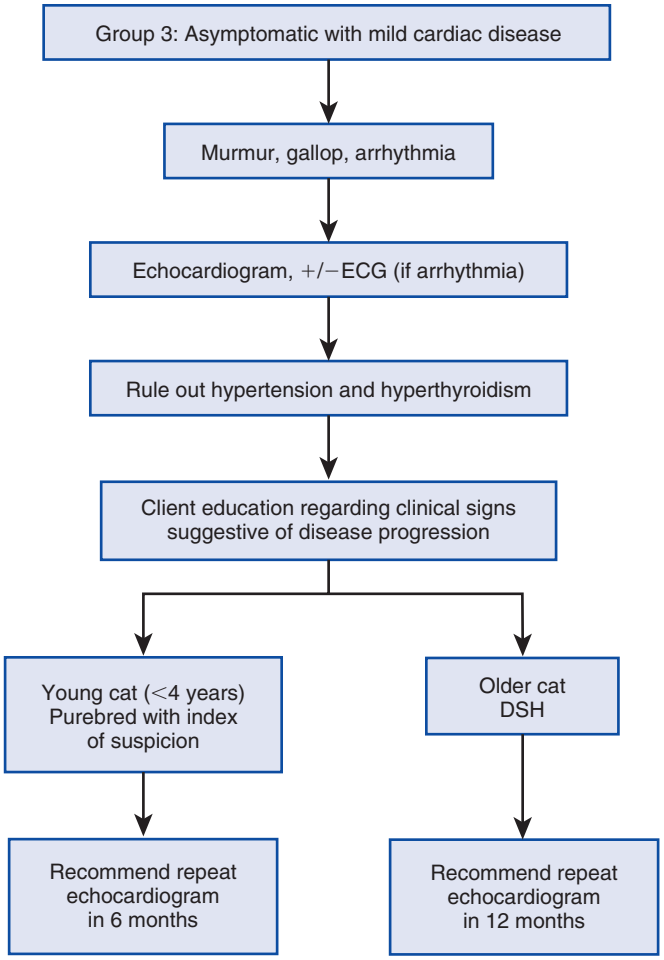

Figure 34-3. Diagnostic and surveillance algorithm for asymptomatic cats with mild cardiac disease.

apeutic recommendations targeting resolution of clinical signs are independent of underlying etiology. The following discussion reviews therapeutic rationale as it relates to clinical stage (symptomatic or asymptomatic) and echocardiographic or ECG abnormalities, highlighting the similarities and contrasting the differences between recommendations for specific cardiomyopathies, including HCM, hypertrophic obstructive cardiomyopathy (HOCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), and unclassified cardiomyopathy (UCM). The therapy of arrhythmogenic right ventricular cardiomyopathy (ARVC) is discussed in Chapter 35.

THERAPEUTIC RATIONALE

Congestive Heart Failure

Clinical signs of CHF in cats, primarily tachypnea and dyspnea, when present should be addressed with appropriate diuresis and intermittent pleurocentesis as required. Abdominocentesis and pericardiocentesis are indicated rarely. Severe signs of congestion (see Figure 34-1) often require emergency evaluation, parenteral furosemide (1 to 2 mg/kg IV q1-4h) and oxygen supplementation until clinical signs begin to resolve (greater than 25 per cent reduction in resting respiration rate), at which time the dose and dosing interval can be reduced (50 per cent) and increased (100 per cent), respectively. Cats that require parenteral furosemide also may benefit from an anxiolytic drug such as butorphanol (0.2 mg/kg IV, IM, SQ) and pleurocentesis and abdominocentesis as indicated. Nitroglycerine paste can be considered adjunctive therapy and used in accordance with attending clinician preference.

Chronic heart failure signs (see Figure 34-1) usually can be managed effectively with furosemide (¼ to ½ of a 12.5-mg tablet, 3.125 to 6.25 mg/cat PO q12-24h) titrated to the lowest dose required to keep the cat free from clinical and radiographic signs of congestion. Clinically, most cats are well controlled chronically with 1 to 2 mg/kg PO q24h and occasionally q12h. Higher doses usually are required initially and can be reduced after the resolution of clinical signs. Some cats may tolerate prolongation of the furosemide dosing interval to once every 2 to 3 days and more rarely discontinuation. In general, the tablet formulation is preferred over the commercially available suspension (alcohol-based) because the suspension is tolerated poorly by many cats. Furosemide suspensions that are non–alcohol-based from formulation pharmacies are well tolerated. Cats that cannot be maintained free of clinical signs of congestion while receiving ½ to one 12.5-mg furosemide tablet (6.25 to 12.5 mg) q12h may benefit from the addition of a second diuretic such as hydrochlorothiazide (⅛ to ¼ of a 25-mg tablet [3.125 to 6.25 mg] q12-24h). If hydrochlorothiazide is initiated, care should be taken to limit overzealous diuresis by reducing the current furosemide dose by approximately 50 per cent. In addition, if potassium supplementation was not necessary previously, it should be initiated at this point to prevent the development of hypokalemia. Potassium supplementation likely will be necessary at this time even if spironolactone is used concurrently. As mono-diuretics, spironolactone (⅛ to ¼ of a 25-mg tablet [3.125 to 6.25 mg], q12-24h) and hydrochlorothiazide are not very potent, but spironolactone may help preserve potassium and thus could be considered adjunctive therapy in any cat with hypokalemia receiving furosemide. Spironolactone should however be used cautiously in combination with an angiotensin-converting enzyme inhibitor (ACEI), particularly if the cat is not receiving furosemide, because of the potential risk of hyperkalemia.

The addition of an ACEI (enalapril or benazepril) long term may help ameliorate clinical signs of congestion in symptomatic patients by limiting plasma volume expansion through inhibition of the renin angiotensin aldosterone system (RAAS).

Severe Ventricular Concentric Hypertrophy and Left Atrial Enlargement

Severe ventricular concentric hypertrophy contributes to clinically significant diastolic dysfunction, and LAE is indicative of clinically significant diastolic dysfunction. Diastolic dysfunction plays a role in all forms of cardiac disease but can be considered an important primary underlying dysfunction in HCM, HOCM, RCM, and UCM. Diastolic dysfunction associated with HCM, and to a lesser extent RCM and UCM, is associated primarily with the severity of myocardial concentric hypertrophy and in the case of DCM, abnormal myocardial energetics. Diastolic dysfunction characteristic of RCM, UCM, and ARVC, and to a lesser extent DCM and HCM, is related additionally to noncardiomyocyte properties such as fibrosis. Historically, agents that improve myocardial relaxation (positive lusiotropes) have represented the cornerstone of therapy in cardiac diseases characterized primarily by diastolic dysfunction with no or minimal systolic dysfunction. Beta-blockers

such as atenolol improve diastolic filling through reduction in heart rate (HR), leading to increased filling times, but provide no direct improvement in relaxation.[12] Calcium-channel blockers such as diltiazem improve diastolic function directly by reducing calcium influx across the cardiomyocyte cell membrane, ultimately reducing systolic intracellular calcium concentrations, and leading to more rapid relaxation.[13,14] However, diltiazem in the nonsustained release formulation suffers from poor owner compliance because of the short 8-hour oral dosing interval. The sustained release products (Cardizem CD 10 mg/kg PO q24h, Dilacor XR 30 to 60 mg/cat PO q12-24h) have a high rate of gastrointestinal complications.[14-16] Available data suggest sustained release diltiazem (Dilacor XR 30 mg/cat daily) and atenolol (1.1 to 2.5 mg/kg PO q24h) may be tolerated poorly and offer no advantage over furosemide alone in symptomatic cats with cardiomyopathy of any etiology with the exception of DCM, which was not evaluated.[16]

More recently, the use of ACEI agents such as enalapril and benazepril has been gaining favor in the treatment of HCM and other cardiomyopathies.[11,17] The rationale for the use of ACEI in HCM involves limiting and potentially reversing myocardial hypertrophy and fibrosis. These effects may normalize left ventricular morphology and improve diastolic function indirectly, leading to a delay of disease progression. Initially, ACEI therapy was contraindicated in HOCM because of the afterload reduction properties of the drugs, which have proven to be rather modest clinically.[18] However, numerous reports in the veterinary literature have demonstrated safety and tolerance of ACEI drugs in cats with HCM, HOCM, or other cardiomyopathies.[11,17]

Based on available data, all forms of cardiomyopathy may benefit from ACEI treatment, if tolerated. HCM, HOCM, and both RCM and UCM (if characterized by significant myocardial hypertrophy) may derive additional benefit from the addition of diltiazem, if tolerated.[13,14,16] Atenolol may be most useful in the setting of sustained tachycardia. Caution must be exercised, however, if diltiazem and atenolol are combined, when atenolol is used in the presence of systolic dysfunction, and when diltiazem or atenolol are used in overtly symptomatic patients. The addition of atenolol or diltiazem in symptomatic patients should be considered only after stabilization.

In the future, drugs that prevent or reverse fibrosis such as aldosterone antagonists (spironolactone) or hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) may warrant investigation in the treatment of diastolic dysfunction in HCM and other cardiomyopathies.

Left Ventricular Outflow Tract Obstruction

Documentation of a moderate to severe Doppler estimated dynamic LVOTO gradient (greater than 50 mm Hg) in HOCM and rarely UCM provides rationale for initiation of atenolol. Acute studies have demonstrated the ability of beta-blockade to reduce the LVOTO gradient in asymptomatic cats with HOCM, and formed the basis historically for the recommendation of atenolol as first-line definitive therapy in HOCM.[19] The decision to add atenolol should be based on client preference and documentation of a moderate to severe Doppler estimated dynamic LVOTO gradient (more than 50 mm Hg). In cats with dynamic LVOTO gradients, atenolol is recommended at an initial dose of ¼ to ½ of a 25-mg tablet PO q12-24h. The dose then is increased until the cat's heart rate under stress (in the hospital) is 160 bpm or less. A follow-up echocardiographic evaluation may be useful to help determine the ability of this therapy to reduce the severity of the dynamic LVOTO gradient. If the patient currently is receiving diltiazem, atenolol should be added with caution (50 per cent reduction in initial atenolol dose). More recent data, however, suggest that with the exception of DCM, which was not evaluated, atenolol may offer no advantage over furosemide alone in symptomatic cats with primary cardiomyopathy, including HCM and HOCM.[16]

Myocardial Infarction

Focal areas of ventricular thinning, hyperechogenicity, hypokinesis, akinesis, or dyskinesis suggestive of myocardial infarcts may be identified in all forms of feline cardiomyopathy. Historically, ACEI treatment has been the cornerstone of therapy in human cardiac diseases characterized by ventricular infarction. More recently, beta-blockade and aldosterone antagonism also have proven beneficial. Feline patients with evidence of an infarction therefore may benefit from treatment with an ACEI (enalapril or benazepril) in combination with atenolol and/or spironolactone. However, caution must be emphasized when combining an ACEI and spironolactone because of the potential for hyperkalemia. This risk may be reduced when these drugs are introduced on a background of furosemide.

Arrhythmias

Chronically, with the exception of ARVC, symptomatic arrhythmias are relatively rare in cats; however, one report cited the presence of cardiac disease in approximately 20 per cent of cats evaluated for sudden death.[20] This suggests that arrhythmias may be an important cause of sudden death in cats with cardiac disease, which may justify primary antiarrhythmic therapy.

Regardless of the underlying form of cardiomyopathy, atenolol can be chosen as initial therapy for ventricular and supraventricular tachyarrhythmias. Atenolol is recommended at an initial dose of ¼ to ½ of a 25-mg tablet PO q12-24h. The dose then is increased until the cat's heart rate under stress (in the hospital) is 160 bpm or less. Caution should be used when initiating beta-blockade (50 per cent dose reduction) in cats already receiving diltiazem or an antiarrhythmic drug with beta-blocking properties such as sotalol. Sotalol (¼ of an 80-mg tablet [10 mg]/cat PO q12h) is a potent antiarrhythmic agent with some ancillary beta-blocking properties that may be particularly useful in the management of life-threatening ventricular arrhythmias or ventricular arrhythmias refractory to atenolol. Both sotalol and atenolol should be initiated at a low dose (1 to 3.125 mg/cat daily) in DCM and other cardiomyopathies if important systolic dysfunction is present. Digoxin (¼ of a 0.125-mg tablet PO q24-48h based on plasma drug monitoring) alone or in combination with atenolol may be useful for the adjunctive treatment of hemodynamically important supraventricular arrhythmias such as atrial fibrillation.

Determination of the ability of any agent to reduce the frequency and severity of arrhythmias can be evaluated by documentation of the resolution of clinical signs if present, and alternatively by reevaluation of an ECG. More comprehensive follow-up would be provided by the use of continuous ambulatory electrocardiography (Holter monitoring).[21,22]

The diagnosis of symptomatic bradyarrhythmias such as atrioventricular block (second degree or third degree) often is associated with an advanced cardiomyopathy, which makes definitive therapy with a pacemaker less rewarding, albeit possible.[23] Asymptomatic bradyarrhythmias may benefit most from additional diagnostic testing to determine the presence and severity of any underlying cardiomyopathy as well as surveillance to evaluate the potential for progression.

Systolic Dysfunction

Systolic dysfunction is associated primarily with DCM and to a lesser extent RCM, UCM, and ARVC. The cornerstone of therapy for systolic dysfunction in dogs and human beings is the administration of ACEI drugs. In light of the reported safety and tolerance of this medication in cats, it should be considered first-line medication in DCM and any cardiomyopathy associated with systolic dysfunction. Digoxin is a weak positive inotrope and neuroendocrine modulator that may be useful as adjunctive therapy in symptomatic DCM.

Historically, taurine deficiency was a recognized etiology of feline DCM. Most cats now identified with DCM have normal plasma and whole blood taurine concentrations (normal nonfasted plasma taurine greater than 60 nmol/ml, at risk less than 30 nmol/ml; normal whole blood taurine greater than 200 nmol/ml, at risk less than 100 nmol/ml). Whole blood taurine concentrations are preferred for evaluation of risk because of their relative stability. Nonetheless, cats documented with systolic dysfunction, even if on an adequate diet, should have a whole blood taurine concentration evaluated. While awaiting test results or in lieu of obtaining a taurine concentration, practitioners should initiate taurine supplementation (500 to 1000 mg/day PO). Taurine is safe and supplementation may be beneficial in idiopathic DCM regardless of plasma taurine concentration.[24-27]

Novel more potent inotropes such as pimobendan (Vetmedin), when available, may prove efficacious as adjunctive treatment in symptomatic feline DCM. Beta-blockade (atenolol) and aldosterone-blockade (spironolactone) eventually may play roles in the management of symptomatic and asymptomatic DCM; however, at this time, addition of these medications should be considered adjunctive and investigational when not used for conventional indications.

Intracardiac Thrombus or Smoke

Heightened risk of ATE must be considered in cats with LAE secondary to any etiology. Substantial risks of embolic complications warranting more aggressive prophylaxis may include severe LAE (LA:Ao greater than 2), previous ATE, left atrial or auricular thrombus, and spontaneous intracardiac echocardiographic contrast (smoke). To date, no evidence supports the efficacy of any agent with respect to limiting the occurrence or recurrence of ATE. Historically, low-dose oral aspirin and oral coumadin have been used. Aspirin (one 80-mg tablet PO twice per week) is safe and reasonably well tolerated. The high risk of complications with oral Coumadin therapy limits its clinical utility, and if used, it should be reserved for patients with very high risk of ATE, such as those with a previous ATE or intracardiac thrombus. More recently, low-molecular-weight heparin (Fragmin, dalteparin sodium 100 IU/kg SQ q12-24h) has been recommended, is not cost prohibitive, and appears to be well tolerated. Low-molecular-weight heparin may offer protection from ATE in high-risk patients and requires no monitoring; however, assessment of partial thromboplastin time or anti-Xa activity may be useful.[28] Given the minimal risk, low-dose aspirin therapy in cats could be considered adjunctive treatment in any cat with atrial enlargement. However, cats with substantial risk of ATE resulting from any etiology could be considered candidates for SQ therapy with low-molecular-weight heparin. However, no proof of efficacy exists of this or any prophylactic antithrombotic agent.

Newer oral antiplatelet drugs capable of irreversible inhibition of ADP platelet membrane receptors such as the thienopyridines, ticlopidine and clopidogrel, likewise may be useful.[29] More detailed discussions of prophylactic antithrombotic therapy and treatment of ATE are found in Chapters 37 and 58.

SUMMARY

To date, no adequately powered prospective clinical studies exist in cats to support definitive therapeutic recommendations regarding the treatment of any cardiomyopathy. Evidence-based therapeutic recommendations await adequately powered prospective clinical trials. Until that time, therapeutic decisions in symptomatic patients should be based on specific clinical signs, characterization of the underlying cardiomyopathy, and individual response to therapy. In asymptomatic patients, therapeutic recommendations should be made based on the presence and severity of the underlying cardiomyopathy. Finally, all therapeutic recommendations should be guided by follow-up evaluations in addition to client and patient preferences.

Establishment of the overall prognosis for cats with symptomatic or asymptomatic cardiomyopathy is limited by a similar lack of prospective data. However, independent of underlying cardiomyopathy, the initial response to therapy in feline patients symptomatic for heart failure predicts long-term outcome. Cats that stabilize easily in the first 2 weeks of therapy often respond favorably for months to years.

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Chapter 35

Arrhythmogenic Right Ventricular Cardiomyopathy

Philip R. Fox

Cardiomyopathies represent the major category of feline cardiovascular diseases. Cardiomyopathy (*cardio-*, heart, *myopathy*, muscle) describes a heterogeneous class of disorders whose dominant feature is a structural abnormality and functional impairment of the heart muscle.[1] As such, these myocardial diseases exclude conditions resulting from valvular, hypertensive, vascular, pericardial, pulmonary, or congenital derangements. A variety of schemes have been proposed to define the cardiomyopathies. The term *idiopathic* (primary) cardiomyopathy has been applied classically to describe the myocardium as the sole source of heart disease when an etiology cannot be identified, whereas *secondary* cardiomyopathy has denoted heart muscle disease resulting from identifiable systemic, metabolic, or nutritional disorders.[1,2] This original classification has been expanded by The World Health Organization/International Society and Federation of Cardiology Task Force to include four types of idiopathic heart muscle disease[3]: hypertrophic, dilated, restrictive, and arrhythmogenic right ventricular cardiomyopathy.[3] Over the past decade, advancements in echocardiographic technology, coupled with its widespread application, have increased clinical awareness and improved diagnostic reliability in the diagnosis of heart disease.

Of the four types of idiopathic heart muscle disease, arrhythmogenic right ventricular cardiomyopathy (ARVC) is the least common in cats.[1,2] Its prevalence is approximately 2 to 4 per cent of myocardial diseases diagnosed in my clinic. Although still underrecognized, diagnosis of this disorder can be improved by rigorous application of diagnostic testing and appropriate clinical awareness.

ETIOLOGY AND PATHOGENESIS

The etiology and pathogenesis of ARVC are unresolved. In human beings, ARVC has been demonstrated to be heritable in some families. Chromosomal loci have been mapped that demonstrate autosomal dominant familial transmission, and a mutation has been identified at the cardiac ryanodine receptor 2 gene (Ryr2) in ARVD type 2.[3-5] Recently, heterozygous mutations in PKP2, which encodes plakophilin-2, also have been described. Plakophilin-1 is an essential armadillo-repeat protein of the cardiac desmosome.[6] ARVC also has been shown to be responsible for sudden, unexpected death in the boxer dog. It is characterized by ventricular arrhythmias, fatty and fibrofatty myocardial replacement, apoptosis, and myocarditis.[7] Pedigree evaluation of boxer dogs with ventricular arrhythmias (and purportedly, ARVC) revealed a familial pattern and suggested that ventricular arrhythmias (and ARVC) were inherited as an autosomal dominant trait in some of these dogs.[8] I have noted familial tendencies of ARVC in cats, but pedigree analysis currently is lacking. Neither the specific gene defects nor the defective coded proteins have been identified in feline ARVC to date.

PATHOPHYSIOLOGY

Progressive atrophy of the right ventricular (RV) myocardium with fibrous and/or fatty replacement underlies morbidity and mortality of ARVC in dogs,[7] cats,[9] and human beings.[10,11] Atrophy of RV myocardium and replacement by fat or fibrofatty tissue undoubtedly reduces cardiac reserve and provokes right-sided congestive heart failure (CHF). Right ventricular dilatation and remodeling alters the geometry and function of the tricuspid valve apparatus, resulting in tricuspid valve insufficiency. Apoptosis is present in a high percentage of cats with ARVC,[9] similar to that reported in human beings[12,13] and dogs[7] with ARVC. As such, the pathogenesis of ARVC may involve inflammation and programmed cell death. Apoptosis and myocarditis in cats with ARVC may contribute to myocyte injury and repair in susceptible cats.[32-33] Fibrofatty replacement of RV myocardium provides the substrate for ventricular arrhythmias. The histopathological changes of ARVC are not confined to the RV, and similar but less marked lesions of myocardial injury and repair may be present in ventricular septum or left ventricular (LV) free wall. Consistent with LV findings in some human ARVC patients, this suggests that the ARVC disease process may progress over time to involve the left ventricle.[10,14,15]

SIGNALMENT

Affected cats range in age from 1 to 20 years old, although right heart failure is detected frequently in middle-age cats.[9] Whether a sex predisposition is present is uncertain. ARVC has been documented in many breeds, and I have identified this condition most commonly in domestic shorthair and Birman cats.

CLINICAL PRESENTATION

The clinical spectrum of ARVC is variable. It is uncertain whether the predominance of heart failure–related cases reflects the true clinical profile of feline ARVC or represents an overrepresentation resulting from patient selection.[9] In cats with heart failure, nonspecific signs may be reported, including lethargy and anorexia. Frequently, the first clinical presentation is for CHF. This occurs in the setting of progressive RV myocardial atrophy and is characterized by right-sided CHF and arrhythmias. Syncope has been documented in association with ventricular tachycardia but is uncommon. Affected cats may display tachypnea, jugular venous distention, abdominal effusion, or hepatosplenomegaly.

PHYSICAL EXAMINATION

Thoracic auscultation usually reveals a pansystolic heart murmur along the right sternal border consistent with tricuspid regurgitation. Arrhythmias and associated femoral arterial pulse deficits may be detected. With right-sided CHF, affected cats may be tachypneic or dyspneic. Many of these animals have distended jugular veins, and some also have ascites and hepatosplenomegaly. The presence of pleural and pericardial effusion may cause heart and lung sounds to be muffled.

RADIOGRAPHY

Thoracic radiographs show enlargement of the right atrium and right ventricle (Figure 35-1). Left atrial enlargement also may be present in some cats. In cases of right-sided heart failure, pleural effusion, ascites, hepatosplenomegaly, and cardiomegaly (associated with pericardial effusion) may be present.[9]

ELECTROCARDIOGRAPHY

A variety of arrhythmias have been recorded in affected cats.[9] Electrocardiographic abnormalities include supraventricular tachyarrhythmias (particularly atrial fibrillation), complex ventricular ectopy including ventricular tachycardia (of right and left ventricular origin), and major conduction abnormalities. Ventricular tachycardia may be sustained in some cases. The frequency of atrial fibrillation is not surprising in view of the severe right atrial enlargement usually associated with RV dilatation.

ECHOCARDIOGRAPHY

The echocardiogram reveals marked right atrial and right ventricular enlargement (Figure 35-2). Additional changes include paradoxical septal motion, abnormal RV muscular trabecular patterns (particularly in the apical RV cavity), and images consistent with localized RV aneurysm formation (i.e., akinetic or

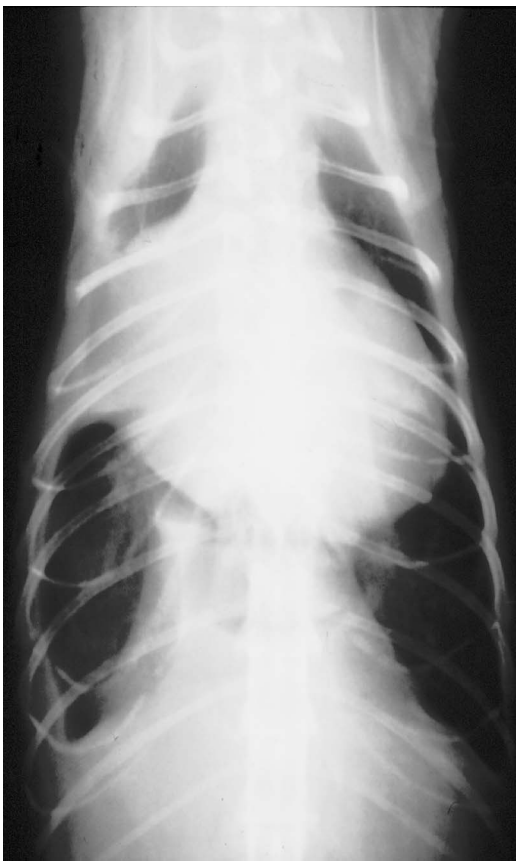

Figure 35-1. Ventrodorsal radiograph from a cat with ARVC and right-sided CHF, severe right atrial and right ventricular enlargement, and pleural effusion.

Figure 35-2. Two-dimensional echocardiogram short-axis view from a cat with ARVC and severe right-sided CHF. Marked dilatation of the right ventricle (RV) has occurred. This chamber is greatly disproportionate to the small left ventricle (LV). *VS*, ventricular septum. (From Fox PR, Maron BJ, Basso C, et al: Spontaneous occurrence of arrhythmogenic right ventricular cardiomyopathy in the domestic cat: a new animal model of human disease. Circulation 102:1863-1870, 2000.)

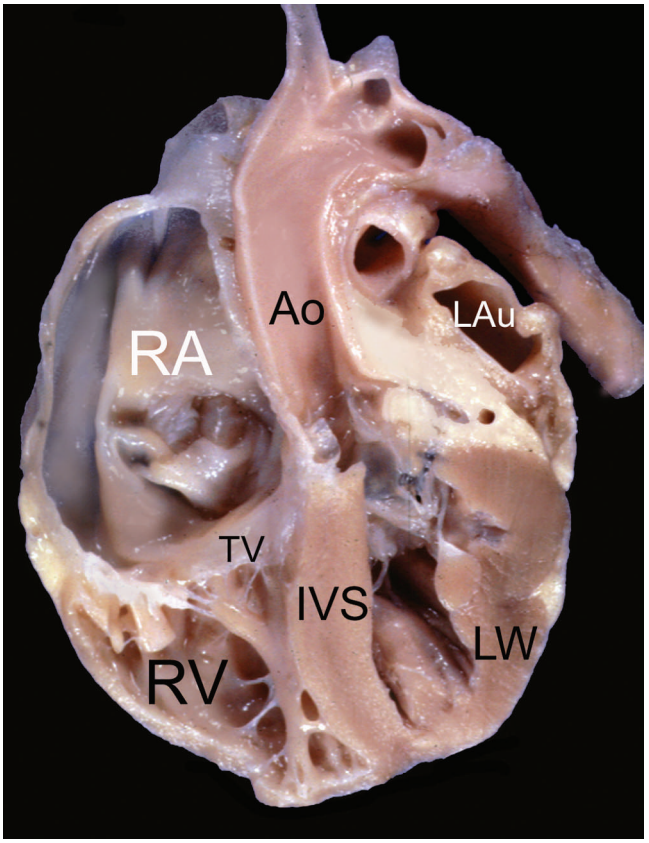

Figure 35-3. Heart from a cat with ARVC with severe dilatation of the right atrium (RA) and right ventricle (RV). *IVS,* interventricular septum. *LW,* left ventricular free wall. *TV,* tricuspid valve. *Ao,* ascending aorta. *LAu,* left auricle.

diskinetic areas with diastolic outward bulging) in the apical or subtricuspid region. Ventricular septal and LV wall thickness at end-diastole, LV end-diastolic and end-systolic cavity dimensions, and per cent fractional shortening (in absence of paradoxical septal motion) generally are within normal ranges. In some cats, left atrial enlargement may be present. Doppler color-flow imaging demonstrates tricuspid regurgitation invariably.

GROSS PATHOLOGY

Morphological abnormalities are striking in feline ARVC[9] and are consistent with those described in human[10,14,15] and canine[7] ARVC patients (Figure 35-3). Typical findings include moderate-to-severe RV dilatation. RV wall thinning is either diffuse or segmental and usually is associated with a flattened appearance of RV wall trabeculae. In addition, RV septo-parietal bands appear prominent. Aneurysms often are present in apical, subtricuspid, and infundibular regions of the RV wall. They may be small or extensive and appear translucent. Right atrial cavity dilatation generally is present and severe, and segments of right atrial walls are markedly thinned. Mural thrombosis occasionally is observed in the RV or LA.[9]

HISTOPATHOLOGY

Histological lesions in feline ARVC[9] closely resembled those characteristic of human[14,15] and canine[7] patients with this

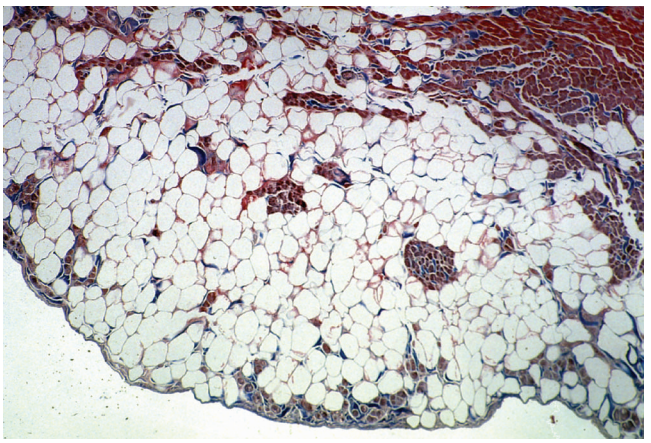

Figure 35-4. Fibrofatty variant of ARVC in a cat with ventricular tachycardia. The fatty replacement of the right ventricular wall is associated with residual myocytes embedded within or bordered by adipose cells. Heidenhain trichrome stain.

condition (Figure 35-4). Most prominent is myocardial atrophy in the RV with cardiac myocytes replaced by adipose or fibrous tissue in two patterns: fibrous (75 per cent) or fibrofatty and fatty (25 per cent). The fibrous or fibrofatty pattern consists of focal or diffuse myocardial atrophy associated with adipose tissue and replacement-type fibrosis, extending from the epicardium toward the endocardium. The fatty pattern within the RV wall and trabeculae is characterized by multifocal areas of adipose cell infiltration with only scant interstitial fibrosis. In both forms, residual surviving myocytes usually are scattered within the areas of fibrosis or fat. Focal or multifocal RV myocarditis is most prevalent in ARVC cats with the fibrofatty pattern and consists mostly of T lymphocytes associated with myocyte cell death and mild-to-severe fibrous tissue deposition. Similar findings also may be present in left and right atrial walls, in addition to LV free wall and ventricular septum. Fatty infiltration occasionally is present in the LV free wall but not in the ventricular septum. Abnormal, intramural small vessels with thickened walls (primarily because of medial hypertrophy) are uncommon. Apoptotic myocytes have been identified by TUNEL (terminal deoxynucleotidyl transferase biotin-dUTP nick end labeling) histochemical investigation in 75 per cent of affected cats.[9] TUNEL is one method for detection of apoptosis at different stages in histological sections of tissue.

DIFFERENTIAL DIAGNOSIS

Careful echocardiographic examination provides a reliable, noninvasive technique to identify structural changes associated with ARVC. Although other forms of spontaneous cardiomyopathy have been documented in domestic cats,[16-20] the morphological features in ARVC cats are unique to this condition and have not been reported in other types of feline myocardial disease. Specifically, severe RV and RA dilatation characterize feline ARVC, and these changes are readily apparent during radiographic and echocardiographic examination. Because tricuspid valvular regurgitation usually is present in the setting of RA and RV dilatation, feline ARVC invariably is misdiagnosed as tricuspid valvular dysplasia. Certain distinctions help differentiate between these conditions. Tricuspid valvular dysplasia, when severe, usually is apparent in the very young cat as a

congenital anomaly. Rarely does tricuspid valve dysplasia result in profound right heart enlargement as does ARVC. Also, features of marked dysplasia of the tricuspid valve apparatus generally are discernable by two-dimensional echocardiography, including direct attachment of valve leaflets to papillary muscles, or papillary muscle or valve leaflet fusion. Other causes of RV dilatation in cats can be differentiated by careful echo-Doppler examination. Right ventricular enlargement attending pulmonic stenosis, tetralogy of Fallot, or other causes of cyanotic heart disease, or pulmonary hypertension, has the additional feature of RV hypertrophy in addition to anomaly-specific lesions. Because the LV generally is unremarkable in ARVC cats, this condition cannot be confused with hypertrophic cardiomyopathy or endomyocardial fibrosis, two diseases characterized by distinctive left ventricular alteration. Moreover, in restrictive cardiomyopathy, these cats do not have severe right heart dilatation and RV wall thinning that typifies cats with ARVC.

THERAPY

Mechanical removal of pleural effusion by thoracocentesis is warranted when dyspnea is present. Standard pharmacological therapy includes the use of diuretics (furosemide, 2 to 4 mg/kg/day; spironolactone, ¼ to ½ of a 25-mg tablet PO daily), angiotensin-converting enzyme (ACE) inhibitors (enalapril, 0.5 mg/kg PO daily), and digoxin (¼ of a 0.125-mg tablet PO q24h or q48h). Symptomatic ventricular tachycardia has been treated safely with sotalol (10 to 20 mg PO q12-24h).

PROGNOSIS

Treatment of cats with right-sided heart failure has been unrewarding, and CHF is rapidly progressive and unresponsive in most cases.

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Chapter 36

HEARTWORM DISEASE

Clarke E. Atkins and Annette L. Litster

Although recognized since 1921,[1] heartworm infection (HWI) in cats has received increasing interest over the last decade. Reasons for this are multiple: an increasing diagnostic armamentarium, an increasingly aware and demanding public, and the development of safe, effective, and broad-spectrum preventative drugs. With this comes the responsibility of understanding the pathogenesis, clinical signs, diagnostic process, treatment, and most important, prevention of HWI in cats.

ETIOLOGY

The domestic cat, although an atypical host, can be parasitized by *Dirofilaria immitis* (HW) with resultant heartworm disease (HWD). The clinical manifestations of the disease are different and more severe in this species, but the infection rate is only 5 to 20 per cent of that of dogs.[1] Experimental infection of cats is more difficult than of dogs; less than 25 per cent of third stage larvae (L_3) reach adulthood. This resistance also is reflected in natural infections, in which feline heartworm burdens are usually less than six, and typically only one to three worms.[1] Other indications of the cat's inherent resistance to this parasite are a shortened period of worm patency, high frequency of amicrofilaremia or low microfilaria counts, and shortened lifespan of adult heartworms (2 to 3 years).[2] Additionally, although some species of mosquito may feed on cats, most prefer dogs, and for a cat to become infected, the mosquito first must have fed on a dog. Nevertheless, studies have shown a prevalence as high as 14 per cent in shelter cats,[1] and a study performed at North Carolina State University revealed HWD in 9 per cent of cats presented with cardiorespiratory signs.[3] Furthermore, antibody testing showed 26 per cent of 100 of these cats to have been exposed to HW.[3] Similar to dogs, some studies have shown male cats to be at higher risk for HWI than females. Aberrant worm migration appears to be a greater problem in cats than in dogs.

PATHOGENESIS

Although not fully understood, the pathological, clinicopathological, and clinical response to infection with *D. immitis* is shown in Figure 36-1. The pulmonary arterial response to adult heartworms is more severe than that of dogs, although pulmonary hypertension has been reported infrequently. Dillon demonstrated pulmonary enlargement within 1 week of transplantation of adult worms, which suggests an intense host-parasite interaction.[4] A severe myointimal and eosinophilic response produces pulmonary vascular narrowing and tortuosity, thrombosis, and possibly hypertension (Figures 36-2 and 36-3, *A*).[5] Because the feline pulmonary artery tree is smaller than that of the dog and has less collateral circulation, embolization, even with small numbers of worms, produces disastrous results, with infarction and even death. Although uncommon, cor pulmonale and right heart failure can be associated with chronic feline HWD and are manifested by pleural effusion (hydrothorax or chylothorax) and/or ascites. The lung per se also is insulted by HWI, with eosinophilic infiltrates in the lung parenchyma (pneumonitis), pulmonary vasculature, and air spaces (see Figure 36-2). The pulmonary vessels may leak plasma and produce pulmonary edema, which has been considered by some investigators to represent acute respiratory distress syndrome (ARDS).[7] If the cat survives the initial insult, type II cells proliferate, replacing damaged type I cells, potentially reducing oxygen diffusion.[4] The end result is diminished pulmonary function, hypoxemia, dyspnea, and cough.

The so-called "sudden death syndrome" typically is attributed to worm death and fulminant pulmonary failure and often pulmonary embolism. Recent research suggests, however, an immune-mediated reaction to HW antigens in the feline shock organ (lung).[6] Fatal respiratory failure probably results when HW antigen is released, which produces alveolar flooding (see Figure 36-3, *A*), periarterial edema (see Figure 36-3, *B*), pulmonary congestion, and acute hypotensive shock.[6]

CLINICAL SIGNS

Cats with HWI may be asymptomatic and, when present, clinical manifestations may be either peracute/acute or chronic.[3,4,7-9] Acute or peracute presentation may follow worm death, embolization, or aberrant migration; signs variably include salivation, tachycardia, shock, dyspnea, hemoptysis, vomiting and diarrhea, syncope, dementia, ataxia, circling, head tilt, blindness, seizures, and death.

More commonly, the onset of signs is less acute. Reported historical findings in chronic feline HWD include anorexia,

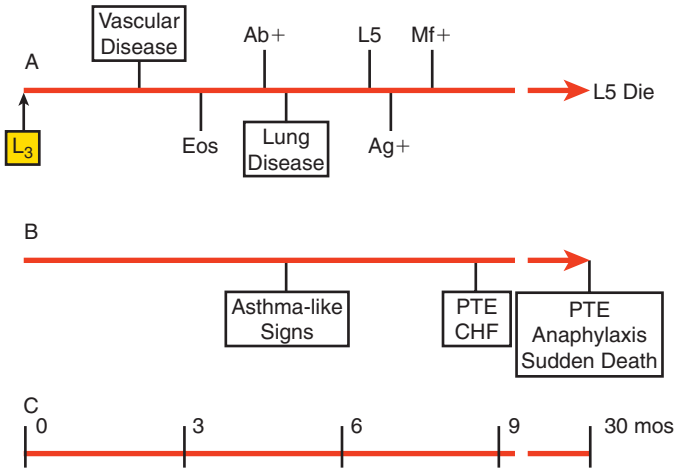
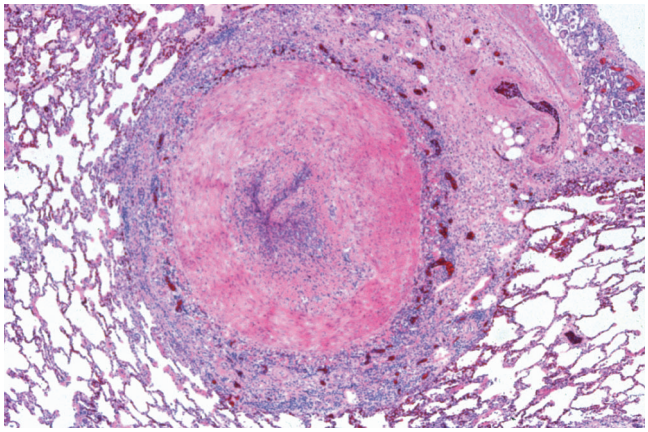


Figure 36-1. Pathological changes and the feline response to heartworm infection **(A),** important clinical findings **(B),** and timeline of heartworm infection **(C)** are estimated from data either known or estimated. Note that the time of infection with third-stage larvae (L_3) is 0 months, and the life expectancy of the heartworm is estimated at 30 months from the time of infection. Vascular disease begins when immature fifth-stage larvae (L_5) enter the vasculature of the lung. This is followed by eosinophilia in some cats, with most becoming positive to the antibody test by 4 months post infection. Radiographically identifiable lung disease is apparent approximately 6 months post infection. Fifth-stage larvae mature at 7 to 8 months post infection, with some cats becoming antigen-positive shortly thereafter, and a few cats becoming microfilaremic 8 to 9 months post infection. Asthma-like signs (cough and wheeze, possibly with dyspnea) may develop from 3 months post infection, with complications such as pulmonary thromboembolism (PTE) and heart failure (CHF, with pleural effusion, often chylous) developing after worms have matured. Cataclysmic signs, including PTE, anaphylaxis, possibly acute respiratory distress syndrome (ARDS), and sudden death may occur with worm death. (*Ab+,* antibody-positive, *Mf+,* microfilaria-positive, *Eos,* eosinophilia, and *Ag+,* antigen-positive.) All times are approximate.



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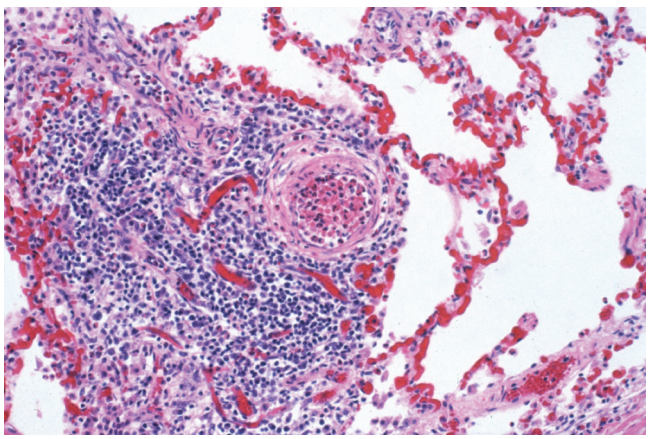


B

Figure 36-2. A, H & E stain demonstrating large pulmonary artery with obstruction of lumen resulting from severe medial smooth muscle hypertrophy and hyperplasia, subintimal and intimal fibrosis, endarteritis, and possibly thrombosis. Also note the periarterial interstitial (probably eosinophilic) pneumonia. **B,** Small pulmonary artery with mild medial hypertrophy. Note the extreme perivascular cuff of inflammatory cells around the vessel, representing an eosinophilic infiltrate.

weight loss, lethargy, exercise intolerance, signs of right heart failure (pleural effusion [rare]), cough, dyspnea, and vomiting. We have found dyspnea and cough relatively consistent findings and, when present, should cause suspicion of HWD in endemic areas.[9]

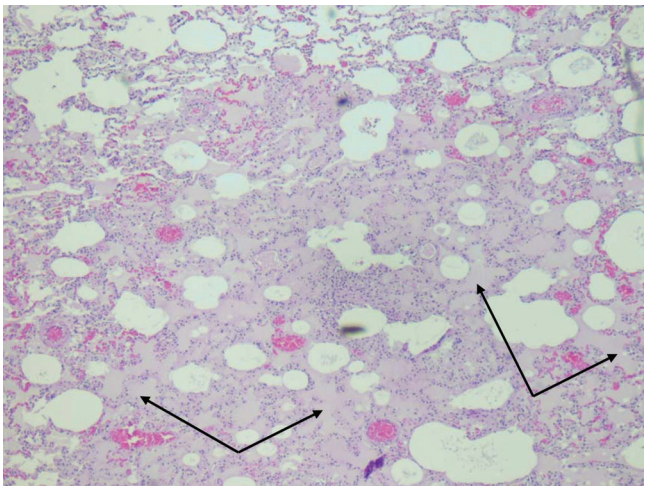
In a report of 50 natural cases (Figure 36-4) of feline HWI seen at North Carolina State University, presenting signs were related most commonly to the respiratory system (32 cats; 64 per cent), with dyspnea (24 cats; 48 per cent) being noted most often, followed by cough (19 cats; 38 per cent) and wheezing.[9] Vomiting was reported in 17 (34 per cent) cats and was noted frequently in 8 (16 per cent). Five (10 per cent) heartworm-infected cats were reported to have exhibited vomiting without concurrent respiratory signs, and vomiting was a presenting sign in seven (14 per cent) of these cats. Neurological signs (including collapse or syncope, which were described in five [10 per cent]) were reported in seven (14 per cent) cats. Five (10 per cent) of the cats were dead at the time of presentation. Murmurs were noted infrequently in cats that did not have concurrent heart disease, independent of HWI. Heart failure was present in one cat; however, this cat had concurrent hypertrophic cardiomyopathy. HWI was considered to be an incidental finding in 14 (28 per cent) of the cats in this study.

Physical examination often is unrewarding, although a cardiac murmur, gallop rhythm, and/or diminished or adventitial lung sounds may be audible. In addition, cats may be thin and/or dyspneic. If heart failure is present, jugular venous distension, dyspnea, and rarely ascites may be detected.

DIAGNOSIS

The diagnosis of HWI/HWD in cats poses a unique and problematic set of issues.[4] First, the clinical signs often are different from those seen in dogs. In addition, the overall incidence in cats is low, so suspicion is lessened; eosinophilia is transient or absent; electrocardiographic findings are minimal; and most cats are amicrofilaremic.

Immunodiagnostic methods also are imperfect in cats because of the low worm burdens (1 to 7, mean = 3)[1] and therefore antigen load. In a study of ELISA antigen tests, positive results were found on sera from 36 to 93 per cent of 31 cats harboring one to seven female HW, with sensitivity increasing as female worm burden increased.[10] Cats with only male worm(s) were not detected as positive. Therefore false-



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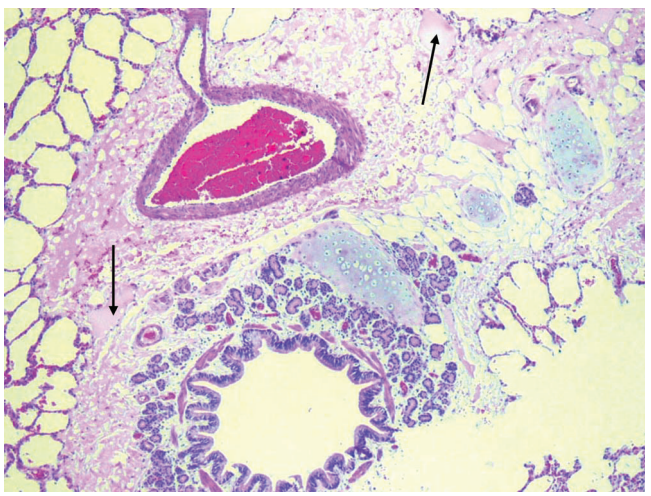


B

Figure 36-3. Pulmonary histopathology from a heartworm-infected cat that died acutely. **A,** Alveolar flooding. Pulmonary artery surrounded by edematous fluid *(arrows),* causing distension of periarterial interstitium. **B,** Periarterial edema. Alveoli are filled with pink proteinaceous fluid *(arrows).*

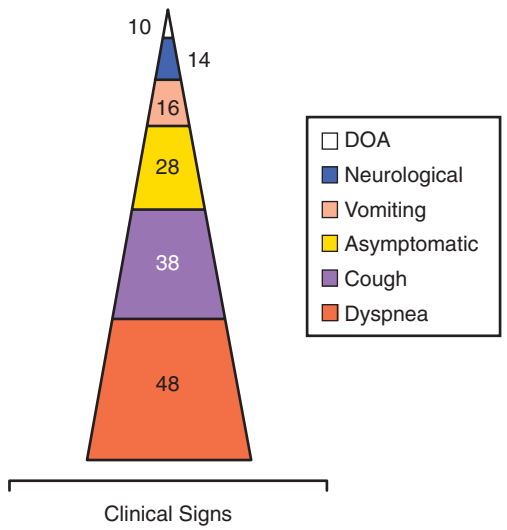


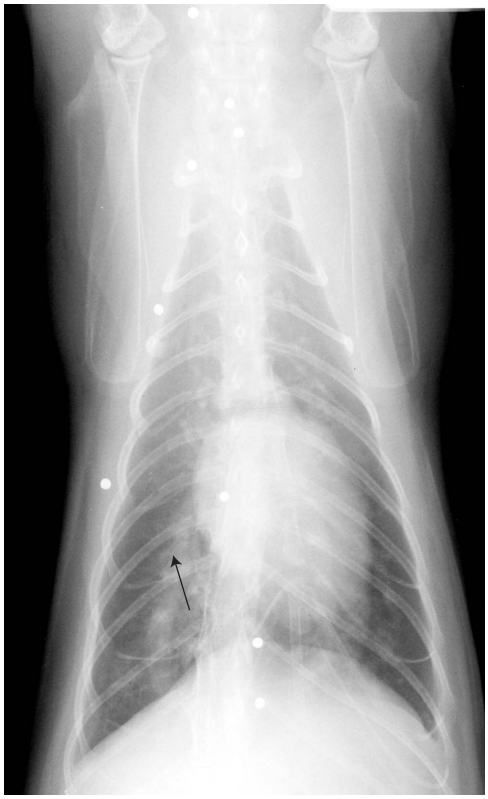
Figure 36-4. Clinical signs (per cent) in 50 cases of naturally acquired feline heartworm infection.[9] (*DOA,* dead on arrival; *asymptomatic,* incidental finding, with signs not heartworm infection–related.)

negative tests occur frequently, depending on test used, maturity and gender of worms, and worm burden. All tests were, however, virtually 100 per cent specific. Infection with accompanying clinical signs may exist before the presence of detectable antigen (from gravid adult females; see Figure 36-1). McCall, Nonglak, Ryan, et al report that, in natural infections, the antigen test detects less than 50 per cent of cases.[11] Snyder, Levy, Salute, et al present differing results from natural infections in which blood was obtained as long as 2 hours post euthanasia. In this study, the antigen test was found to be more sensitive than previous reports (74 per cent).[12] Recently an antigen test has been marketed "for cats" (IDEXX SNAP Feline Heartworm Antigen Test, IDEXX Laboratories, Westbrook, ME). This is an adaptation of the canine test with a reported increase in sensitivity of 15 per cent over conventional antigen tests.

Although not specific for *mature* infections, heartworm antibody tests are of use in the detection of *exposure* to (and partial development of) heartworms. These tests therefore are useful to determine cats at risk for HWI and to determine the potential for HWI in antigen-negative cats, in which HWI is a consideration. We use a negative antibody test to "rule out" HWI in cats with HWD-compatible signs. It must be kept in mind nevertheless that in one study, 14 per cent of cats with a proven natural infection were shown to be antibody-negative.[8] Furthermore, although infrequent (2 per cent), cats may be antibody-negative and antigen-positive, leading some investigators to suggest that the two tests be run in tandem when HWI is suspected. However, for routine screening, the antibody test is the preferred test. An "in clinic" feline heartworm antibody test (Heska Solo Step FH, Heska Corporation, Fort Collins, CO) is now available.

Thoracic radiographs (Figure 36-5) have been suggested as a screening test for HWI in cats. However, Schafer and Berry showed that the most sensitive radiographic criterion (left caudal pulmonary artery greater than 1.6 times the width of the ninth rib at the ninth intercostal space) was detected in only 53 per cent of cases (see Figure 36-5, *A*).[13] Furthermore, even though most cats with clinical signs have some radiographic abnormality, the findings often are not specific to HWD. A study by Selcer, Newell, Mansour, et al demonstrated that radiographic findings often were transient and that radiographic abnormalities were found in cats that ultimately resisted maturation of HW and in which no worms were found on postmortem examination (i.e., "false positive").[14] Radiographic findings include enlarged caudal pulmonary arteries, often with ill-defined margins, pulmonary parenchymal changes including focal or diffuse infiltrates (interstitial, broncho-interstitial, or alveolar), perivascular density, and occasionally, atelectasis (Figure 36-6). Pulmonary hyperinflation also may be evident (see Figure 36-5, *B*). Pulmonary angiography also has been used to demonstrate radiolucent linear intravascular "foreign bodies," in addition to enlarged, tortuous, and blunted pulmonary arteries with loss of arborization.

The Vertebral Heart Scale (VHS) method has been used to assess the effect of HWI objectively on the size of thoracic structures in feline radiographs. It was found that the caudal vena cava (lateral view) and right pulmonary artery (DV/VD view) were enlarged significantly in heartworm-infected cats, compared with a control group of radiologically normal cats. Overall cardiac size also was increased in both lateral and DV/VD radiographs of heartworm-infected cats. Objective



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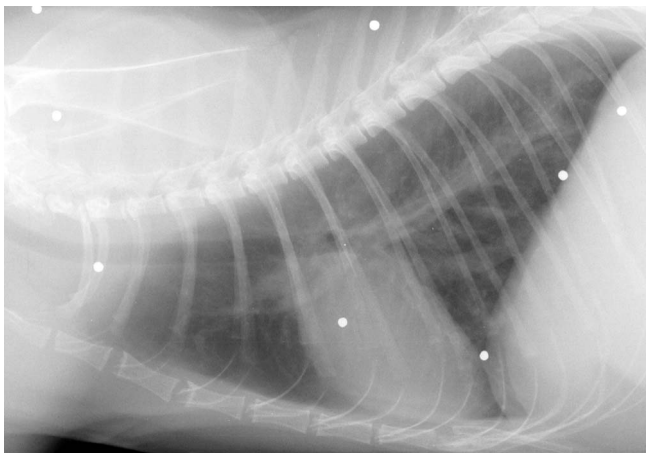

B

Figure 36-5. A, Dorsoventral thoracic radiograph from a cat with heartworm disease. Pulmonary changes are not dramatic, but the right caudal lobar pulmonary artery is enlarged (more than 1.6 times the width of the ninth rib at the ninth intercostal space; *arrow*). The opposite pulmonary artery is somewhat tortuous. **B,** Lateral thoracic radiograph from the cat referred to in Figure 36-5, *A*. A fine interstitial pattern exists in the caudal lung lobes and the chest is mildly hyperinflated. Because the radiographic patterns seen with feline bronchial disease and feline heartworm disease are similar, attempts to differentiate between them often cause confusion (see Chapter 39).

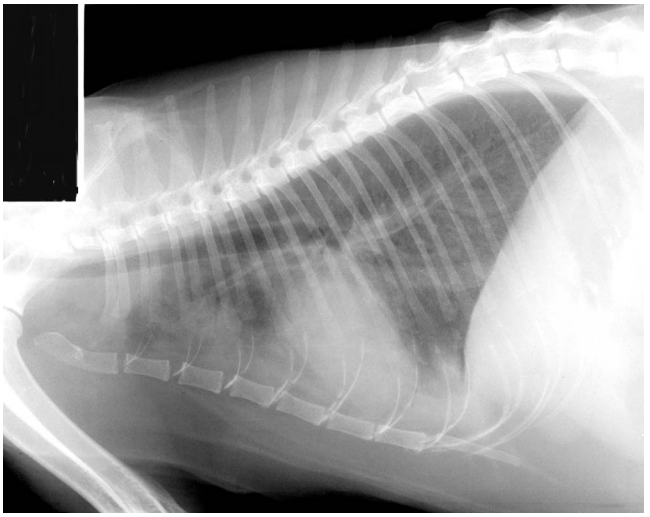

Figure 36-6. Lateral thoracic radiograph of a cat with severe respiratory distress and heartworm disease. Note the alveolar infiltrate in the ventral thorax and the less severe interstitial infiltrate more dorsally in the caudal lung lobes. This severe lung disease probably is due to heartworm death and may represent an acute anaphylactic reaction.

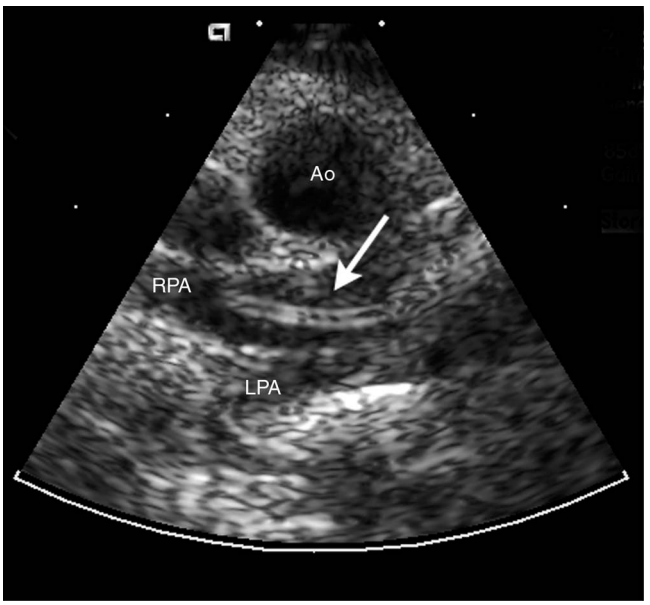

Figure 36-7. A short-axis, two-dimensional echocardiogram obtained from an 18-year-old castrated male feline cancer patient with an asymptomatic cardiac murmur. An adult heartworm can be identified as two echo-dense parallel lines in the right pulmonary artery *(arrow)*. (*Ao,* aorta; *RPA,* right pulmonary artery; *LPA,* left pulmonary artery.)

assessment such as this may be useful in disease staging, to evaluate the severity of disease, and in ongoing case management to assess the efficacy of treatment.[15]

Echocardiography (Figures 36-7 and 36-8), in our experience, is more sensitive in cats than in dogs.[3,16] Typically, a "double-lined echodensity" is evident in the main pulmonary artery, one of its branches, the right ventricle, or occasionally at the right atrioventricular junction. Atkins, DeFrancesco, Miller, et al found HW echocardiographically in 78 per cent of nine symptomatic clinical cases,[3] as did Selcer, Newell, Mansour, et al in 16 experimentally infected cats.[14] Heartworms inhabit the main pulmonary artery or its branches most commonly, which requires some expertise and an index of suspicion from the sonographer. HWI can be missed by ultrasound when worms are immature (hence, smaller) or when they have

died and become compacted into the more distal pulmonary arteries.

We use a combination of serological, radiographic, and echocardiographic modalities commonly in making a diagnosis of HWI in cats. Algorithmic overviews of this approach in routine screening (Figure 36-9) and for the diagnosis of HWI when it is suspected (Figure 36-10) are provided.

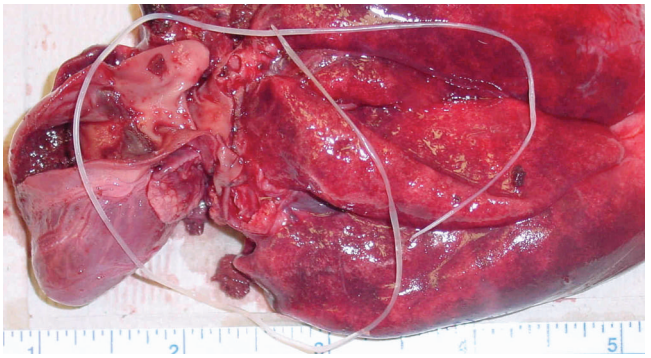

Figure 36-8. Postmortem specimen from the cat referred to in Figure 36-7. Note the size (28 cm) of the female heartworm relative to the lung and pulmonary vasculature, which demonstrates why heartworms are detected relatively easily with ultrasound in cats.

PREVENTION

The question arises as to whether heartworm prophylaxis is warranted for cats because they are not the natural host and because the incidence of infection is relatively low. Necropsy studies of feline HWI in the southeastern United States have yielded a prevalence of 2.5 to 14 per cent with a median of 7 per cent (Figure 36-11).[1] A consideration of the question of institution of prophylaxis should include the fact that this prevalence approximates or even exceeds that of FeLV and FIV infections in comparable populations.[16] A 1998 nationwide antibody survey of more than 2000 largely asymptomatic cats revealed an exposure prevalence of nearly 12 per cent (Figure 36-12).[18] Although outdoor cats are at greater risk for HWI,[17] nearly one third of cats diagnosed with HWD at North Carolina State University were housed solely indoors, based on owners' information.[9] Last, the consequences of feline HWD are potentially dire, with no clear therapeutic solutions. Therefore we advocate preventative therapy in cats in endemic areas. Now three drugs with FDA approval are available and are marketed for use in cats. Ivermectin is provided in a chewable formulation, milbemycin as a flavored tablet, and selamectin, a broad-spectrum parasiticide, comes in a topical formulation. The spectrum in addition to the formulation of these products varies, and hence the clients' individual needs are met easily

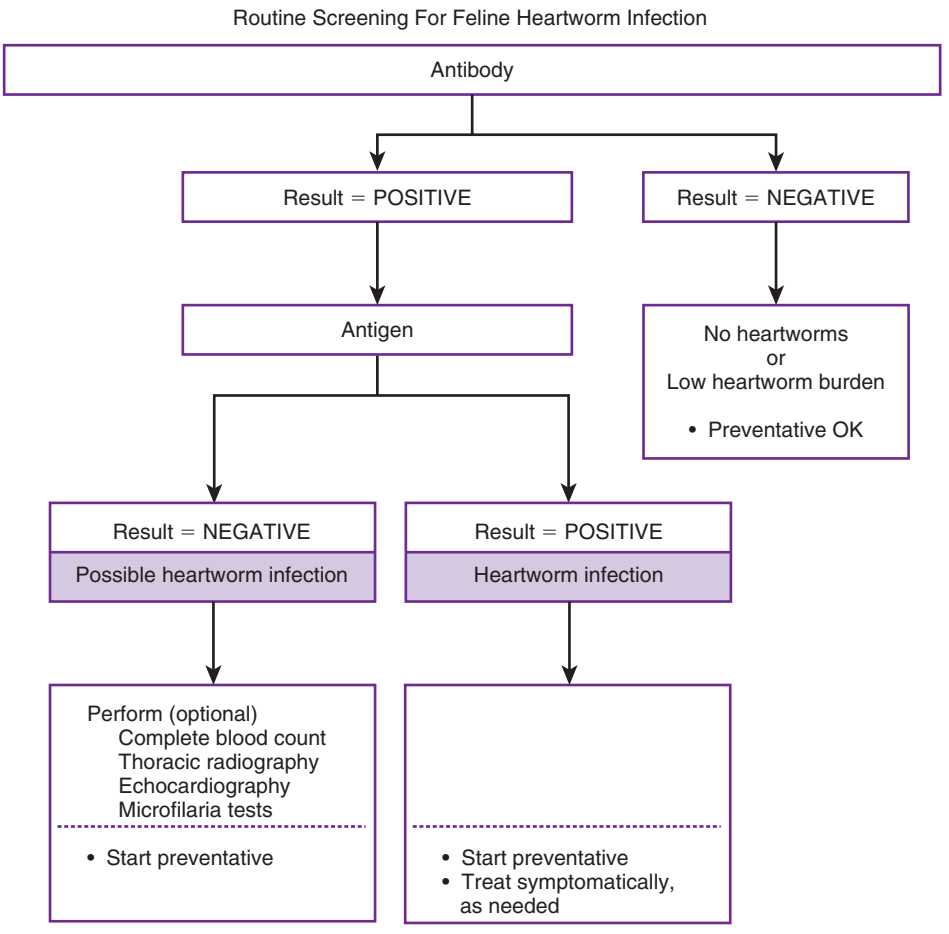

Figure 36-9. An algorithm demonstrating our approach to screening cats for heartworm infection.

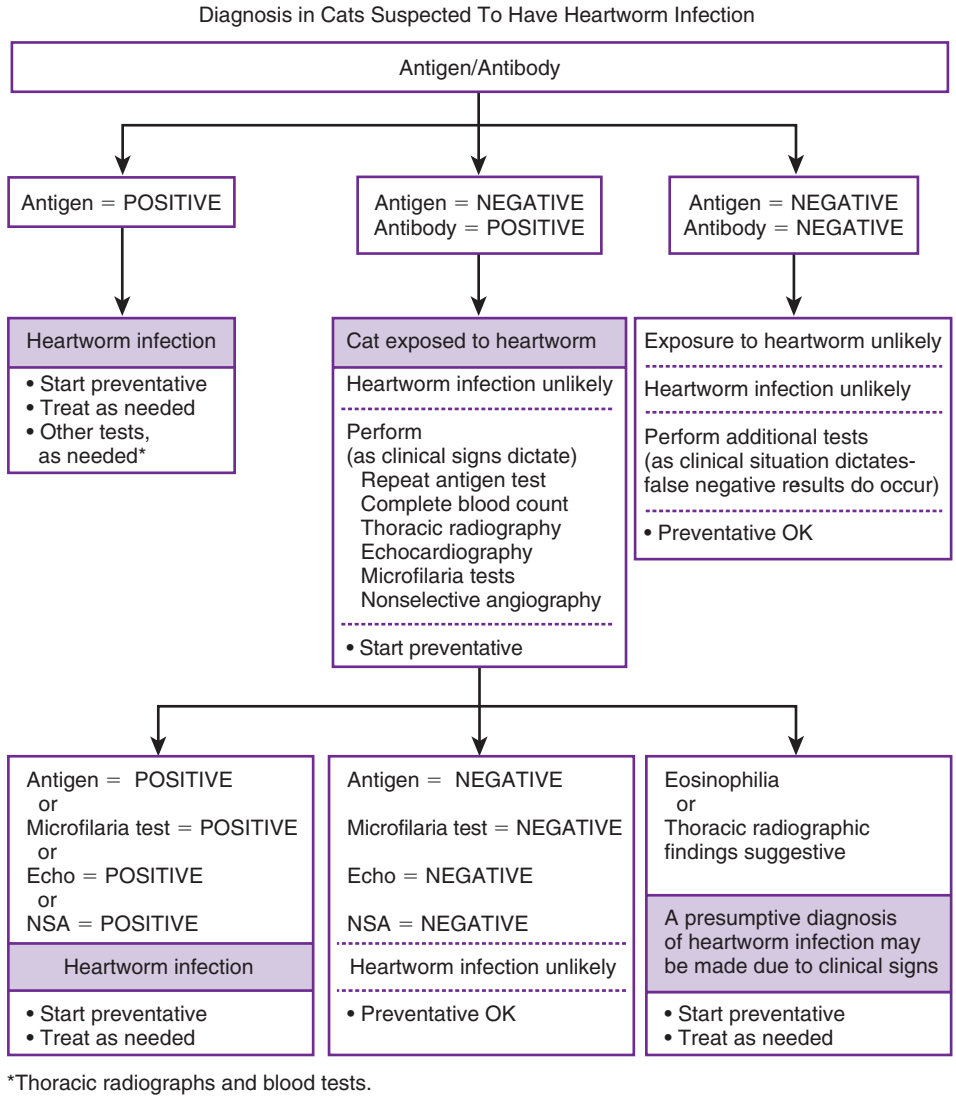

Figure 36-10. An algorithm demonstrating our approach to the diagnosis of heartworm infection in cats in which infection is suspected. *NSA,* Nonselective angiogram.

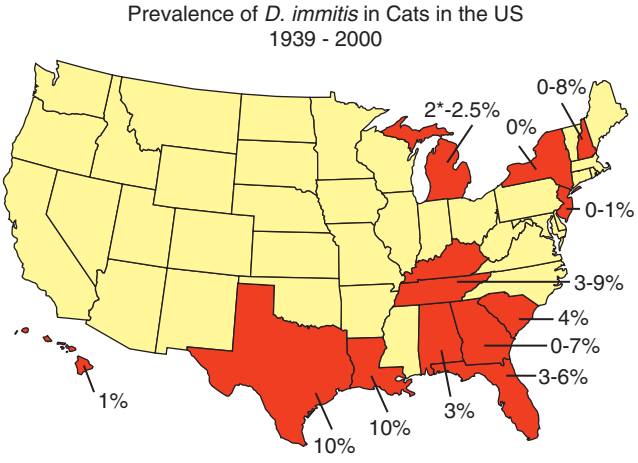

Figure 36-11. Necropsy prevalence of heartworm infection in shelter cats.[1] The shaded states are those in which such studies have been completed. *One Michigan study, which showed a prevalence rate of 2 per cent, was an antigen study.

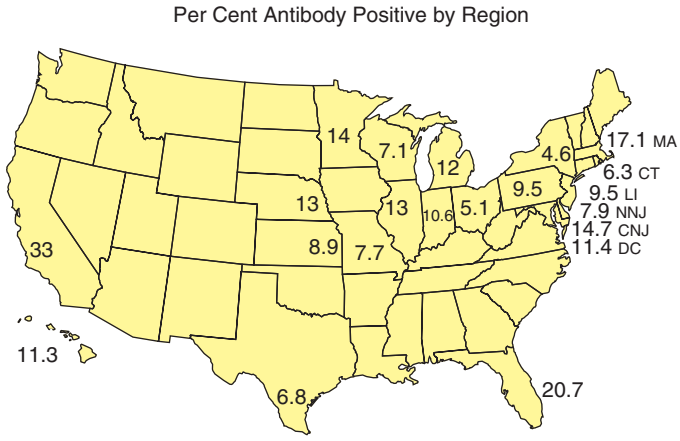

Figure 36-12. Prevalence (per cent) of heartworm exposure in more than 2000 largely asymptomatic cats in 19 states (21 regions).[18] (*NNJ,* north New Jersey; *CNJ,* central New Jersey; *LI,* Long Island, NY.)

Table 36-1 | **Comparisons of Macrolides Currently in Use in Cats for Heartworm Prevention**

DRUG	HW	HOOK	WHIP	ROUND	TAPE	FLEA/EGGS	TICK	SARCOPTES	EAR MITES
Ivermectin	+	+							
Milbemycin	+	+		+					
Selamectin	+	+		+		+/+	+	+	+

in most cases (Table 36-1). The risk of an adverse reaction to dying microfilariae is small because of the microfilarial "slow-kill" property of most macrolide preventatives (with milbemycin being the exception), and because most cats are amicrofilaremic or have low microfilarial burdens. Nevertheless, precaution should be taken (i.e., in-clinic administration of first macrolide dose) in known microfilaremic cats.

TREATMENT

The use of arsenical-adulticides is problematic. Thiacetarsemide, if available, poses risks even in normal cats. Turner, Lees, and Brown reported death resulting from pulmonary edema and respiratory failure in 3 of 14 normal cats given thiacetarsemide (2.2 mg/kg twice over 24 hours).[19] Dillon, Cox, Brawner, et al could not confirm this acute pulmonary reaction in 12 normal cats receiving thiacetarsemide, but one cat did die after the final injection.[20] More importantly, a noteworthy, although unquantified, percentage of cats with HWI develop pulmonary thromboembolism after adulticidal therapy.[4,7,8] This occurs several days to a week after therapy and often is fatal. In 50 cats with HWI, seen at North Carolina State University, 11 received thiacetarsemide. No significant difference existed in survival between those receiving thiacetarsemide and those receiving symptomatic therapy.[9]

Data on melarsomine in experimental (transplanted) HWI in cats are limited and contradictory. Although an abstract report exists in which one injection (2.5 mg/kg; 50 per cent of the recommended canine dosage) of melarsomine was used in experimentally infected cats without treatment-related mortality, the worm burdens after treatment were not significantly different than those found in untreated control cats.[21] Diarrhea and heart murmurs were noted frequently in treated cats. A second abstract report, using either the standard canine protocol (2.5 mg/kg twice over 24 hours) or a "split-dosage" protocol (one injection, followed by two injections, 24 hours apart, in 1 month), gave more favorable results.[22] The standard treatment and split-dosage regimens resulted in 79 per cent and 86 per cent reduction in worm burdens, respectively, and no adverse reactions occurred.

Although promising, these unpublished data must be interpreted with caution because the transplanted worms were young (less than 8 months old and more susceptible); the cats may not have had time to develop antibodies to HW antigens, therefore reducing the risk of a possible anaphylactic reaction; and the control cats experienced a 53 per cent worm mortality (average worm burden was reduced by 53 per cent by the act of transplantation). Additionally, the clinical experience in naturally infected cats has been generally unfavorable, with an unacceptable mortality. Because of the inherent risk, the lack of clear benefit, and the short life expectancy of heartworms in this species, we do not advocate adulticidal therapy in cats.

Surgical removal of heartworms has been successful and is attractive because it minimizes the risk of thromboemboli. The mortality rate reported in the only published case series was, unfortunately, unacceptable (two of five cats).[23] Further refinements to this procedure may hold promise for the future, however.

Cats with HWI should be placed on a monthly preventative and short-term oral corticosteroid therapy used to manage respiratory signs. If signs recur, alternate-day corticosteroid therapy (at the lowest dosage that controls signs) can be continued indefinitely. For respiratory emergencies, oxygen, corticosteroids (dexamethasone at 1 mg/kg IV or IM, or prednisolone sodium succinate at 50 to 100 mg IV/cat) and bronchodilators (aminophylline at 6.6 mg/kg IM q12h, theophylline sustained release at 10 mg/kg PO, or terbutaline at 0.01 mg/kg SC) may be employed. Bronchodilators have therapeutic logic, based on the ability of agents, such as the xanthines (aminophylline and theophylline), to improve function of fatigued respiratory muscles. In addition, radiographic demonstration of hyperinflated lung fields may indicate bronchoconstriction, a condition for which bronchodilators would be indicated. Nevertheless, we do not use bronchodilators routinely in the management of feline HWD.

The use of aspirin has been questioned, because vascular changes associated with HWI consume platelets, increasing their turnover rate and effectually diminishing the antithrombotic effects of the drug. Conventional doses of aspirin did not prevent angiographically detected vascular lesions.[24] Dosages of aspirin necessary to produce even limited histological benefit approached the toxic range. However, because therapeutic options are limited; because aspirin at conventional doses (80 mg PO q72h) generally is harmless, inexpensive, and convenient; and because the quoted studies were based on relatively insensitive estimates of platelet function and pulmonary arterial disease (thereby possibly missing subtle benefits), we continue to advocate the administration of aspirin to cats with HWI. Aspirin is *not* prescribed concurrently with corticosteroid therapy.

Because the vast majority of infected cats are amicrofilaremic, microfilaricidal therapy is unnecessary in this species. Management of other signs of HWD in cats largely is symptomatic.

PROGNOSIS

In the aforementioned study of 50 cats with natural HWI, at least 12 cats died of causes other than HWD.[9] Seven of these patients and two living cats were considered to have survived heartworm disease by living 1000 days beyond diagnosis (i.e., longer than the heartworms' life expectancy).[9] The median survival time for all heartworm-infected cats living beyond the day of diagnosis (n = 39) was 1460 days (4 years; range 2 to 4015 days), whereas the median survival time of all cats (n = 48 with

adequate follow-up) was 540 days (1.5 years; range 0 to 4015 days). Survival of 11 cats treated with sodium caparsolate (mean = 1669 days) was not significantly different from that of the 30 cats managed without adulticide (mean 1107 days). Likewise, young age (3 years of age or younger), presence of dyspnea, cough, ELISA-positivity for heartworm antigen, presence of echocardiographically identifiably worms, or gender of the cat did not appear to affect survival.[9] The effect of HWI on survival has been compared with that of other cardiovascular diseases.[25] Overall, the prognosis for HWI in cats is comparable with that of hypertrophic cardiomyopathy, the most benign of primary feline heart diseases.

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Chapter 37

Prevention and Management of Thromboembolism

Daniel F. Hogan

BACKGROUND

Arterial thromboembolism (ATE), also called systemic arterial thromboembolism (SATE) or feline arterial thromboembolism (FATE), most commonly is associated with underlying myocardial disease including hypertrophic, dilated, restrictive, and unclassified/ischemic cardiomyopathy.[1-9] A clinical association apparently exists between ATE and neoplasia. Studies have identified a small number of cats (2.5 to 6 per cent) with ATE and neoplasia that did not have underlying cardiac disease.[3,6,9,10] Most of these cats had pulmonary neoplasia, which also has been associated with increased risk for thrombosis in human cancer patients.[11] Paraneoplastic thrombocytosis also has been identified in human beings and cats, although whether this translates into an increased risk for thrombosis is unclear.[10,12,13] Last, although not studied in cats, platelets from dogs with neoplasia have been shown to have increased responsiveness to agonists, which suggests increased platelet sensitivity.[14] Some speculate that these neoplasia-associated ATE cases represent tumor embolism. Although this may be feasible, no neoplastic cells were identified in serial sections of the arterial embolus in at least one case.[10] However, because of the unique access to the systemic circulation, thrombus associated with a pulmonary tumor may be the origin of the embolus.

Because of the high prevalence of underlying cardiac disease and similarity to cardiogenic embolism in human beings, we propose to refer to this condition as cardiogenic arterial thromboembolism (CATE) or simply cardiogenic embolism (CE). Cardiogenic embolism is uniquely different from arterial thrombosis, which is the most common cause of vascular events in human beings, including acute myocardial infarction (AMI), thrombotic stroke, and peripheral arterial disease (PAD). Arterial thrombosis results from in situ thrombus formation at a site of vascular disruption (usually a fractured atherosclerotic plaque) and is classified as a platelet-rich clot (PRC). Cardiogenic embolism is the result of vascular obstruction by a fragment of an intracardiac fibrin-rich thrombus with no underlying vascular disease (see section on pathogenesis). Cats rarely experience true arterial thrombosis, so the focus of this discussion is on CE.

The occurrence rate for CE secondary to hypertrophic cardiomyopathy in cats has been reported to be from 12 to 17 per cent.[4,7] According to the veterinary medical data base (www.vmdb.org), CE occurs in 0.1 per cent of all cats that present for medical care at North American veterinary teaching hospitals.[15] Male cats are overrepresented at 67.7 per cent (OR [odds ratio] = 2.02) (58.2 per cent neutered, OR = 5.07); this is significantly different from the general population (50.9 per cent, 31.37 per cent neutered). However, this parallels the frequency of males with underlying myocardial disease (65.0 per cent, 57.9 per cent neutered) and most likely accounts for the gender bias for CE. Domestic breeds were most common (84.3 per cent), but this frequency is similar to the general population (86.7 per cent) and underlying myocardial disease (81.4 per cent). Breeds that appear to have an increased risk include Ragdoll (0.63 per cent, OR = 8.23), Birman (1.25 per cent, OR = 5.08), Tonkinese (0.31 per cent, OR = 2.28), Abyssinian (1.57 per cent, OR = 2.12), and Maine coon (0.94 per cent, OR = 1.21). However, the frequency of CE in the Maine coon breed is less than that seen for underlying myocardial disease (1.46 per cent, OR = 4.31), which could suggest some protective characteristic for CE in this breed. The mean frequency of CE in cats with myocardial disease was 6 per cent (HCM = 6 per cent, DCM = 5 per cent, RCM = 6 per cent, nonspecific myocardial disease = 7 per cent). Retrospective studies have identified similar patterns with respect to gender and breed in which Ragdolls, Birmans, and Abyssinians were overrepresented.[9] Domestic short-haired and long-haired breeds, Persian, Himalayan, Siamese, and Maine coon breeds were identified frequently but were not considered to have a greater frequency for CE than in the general population.*

*References 3,4,6,7,9,16.

In human beings, CE is caused by atrial fibrillation, cardiomyopathy (dilated, hypertrophic, restrictive, ischemic), AMI, mitral valve stenosis, and artificial cardiac valves.[17] Occurrence rates vary depending upon underlying cardiac disease. The brain, eyes, coronary circulation, spleen, bowel, and aortic bifurcation represent the most common sites of infarction.[18] Cardiogenic thromboembolic stroke (CTES), the most common and clinically significant form of CE, is seen in approximately 15 per cent of all human cardiomyopathic patients, with dilated (18 per cent) and restrictive forms more common than hypertrophic (7 per cent).[19-21] The most common site for CE in cats is the aortic trifurcation, with brachial, cerebral, renal, and splanchnic infarctions reported occasionally.[9]

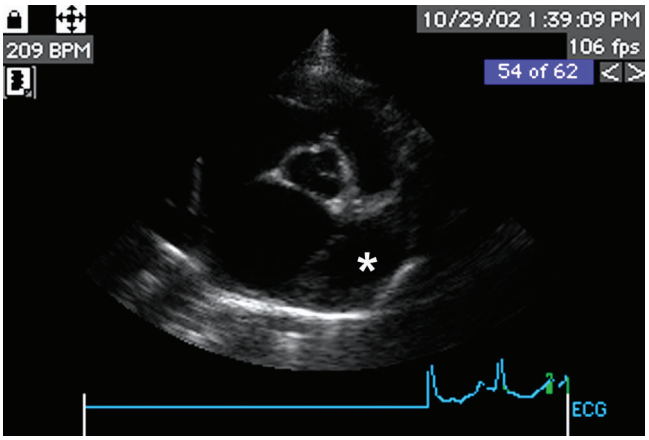
PATHOGENESIS

Cats with myocardial disease are at risk for developing intracardiac thrombi as a result of underlying mechanisms fulfilling all aspects of Virchow's triad. These include blood stasis, endothelial injury, and a hypercoagulable state. Impaired left ventricular filling elevates left atrial pressure, which results in left atrial dilation and blood stasis that can be visualized as spontaneous contrast or "smoke" on echocardiographic examination. As the atrium dilates, the endothelial surface stretches and areas of separation exposing subendothelial collagen or injury (fibrosis) can form, which allows platelet adhesion with subsequent activation and aggregation. Finally, cats with cardiac disease have been reported to have altered platelet aggregation recognized as increased response to ADP in one study,[22] whereas another study demonstrated reduced response to ADP and increased response to collagen.[23]

Although this may seem contradictory, studies indicate that some cardiovascular diseases result in partial activation of platelets in human beings and dogs.[24-29] These circulating partially activated platelets have reduced function, may not be able to respond normally to agonists, and have reduced survival times. Therefore cardiac disease in cats may result in hyperaggregable (hypersensitive) and hypoaggregable platelets. Similar changes in platelet function have been identified in human beings with HCM.[30] Although more related to arterial thrombosis, a similar situation has been seen in human patients with PAD, in which they have increased platelet sensitivity and greater aggregation response to agonists.[31,32] Another possible answer is that feline platelets are extremely sensitive and can become activated during blood collection before stimulation in the aggregation chamber. This results in a reduced aggregation response and is especially dramatic with ADP.

FORMATION OF MURAL THROMBUS

The initiation of the mural thrombus begins with the exposure of subendothelial collagen along the dilated atrial wall. This results in a sequence of platelet responses, including adhesion to the subendothelial site, activation and aggregation with release of agents with proaggregating and vasoconstrictive properties, and initiation of the coagulation cascade. For these reasons, the early thrombus is platelet rich but then becomes fibrin rich as the thrombus grows (Figure 37-1). As the thrombus matures, it becomes lamellated and superficial portions can break off and form the emboli that travel to distant sites, where their size exceeds vessel diameter.



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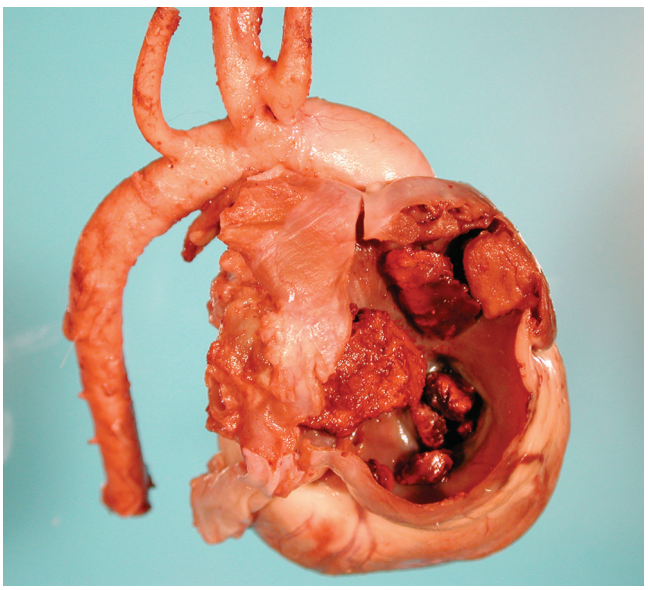


B

Figure 37-1. A, Two-dimensional echocardiographic image demonstrating a large mural thrombus (*) within the left auricle of a cat with ischemic cardiomyopathy. **B,** Multiple large antemortem thrombi can be seen within the right atrium and auricle of a cat with tetralogy. (Dorsal aspect, lateral, and dorsal wall of right atrium removed.)

ISCHEMIC NEUROMYOPATHY

Although cerebral, renal, and splanchnic embolism occur occasionally, aortic trifurcation and brachial embolism account for the vast majority of cases and result in ischemic neuromyopathy (INM). A major contributing factor of INM appears to be the release of vasoactive substances from activated platelets, reducing collateral flow around the site of obstruction. Similar factors also have been identified in human beings suffering from thrombotic stroke, CE, CTES, and pulmonary thromboembolism.[33-38]

Experimental models have revealed that simple ligation of the distal feline aorta does not result in reduced blood flow to the hind limbs or the classical clinical signs of INM.[39-41] Under such conditions, blood flow is maintained through an extensive collateral circulation in the vertebral system and epaxial muscles. However, when a thrombus is created within the

isolated aortic segment, loss of this collateral circulation occurs and clinical signs of INM are evident. This same effect also can be seen when serotonin is injected into the isolated aortic segment in the absence of a thrombus, which suggests a primary role for serotonin in the pathogenesis of INM.[40]

The role of serotonin is supported further by results of a study that revealed the maintenance of collateral circulation and absence of clinical signs of INM with a thrombus within an isolated aortic segment when preadministration of the serotonin antagonist cyproheptadine was used.[42] Evidence also exists that serotonin released from activated cat platelets stimulates sympathetic afferent fibers and may be responsible at least partially for the pain associated with ischemia.[43] More than 98 per cent of circulating serotonin is located in platelets and is released when platelets are activated. Another study suggested that serotonin was not the vasoactive substance but an agonist for platelet release of thromboxane A_2 that was responsible for the loss of collateral flow.[44] In that study, a single high dose of aspirin (650 mg, eightfold higher than standard dose) to cats before thrombus formation in the aortic segment resulted in improved collateral flow. Further support for this can be found in a study that demonstrated aspirin reduced thromboxane but not serotonin release from cat platelets when stimulated with collagen.[45] Similar platelet responses have been seen in human beings.[46]

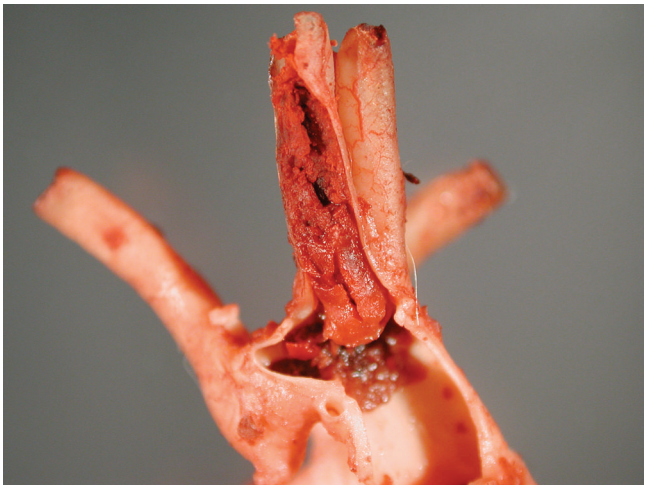
CLINICAL SIGNS

Clinical signs attributable to CE depend on the infarcted vascular bed. Renal infarction can result in acute renal failure and renal pain, whereas mesenteric infarction can manifest with abdominal pain and vomiting. Profound neurological deficits and seizures can be associated with cerebral infarctions and sudden death in severe cases (Figure 37-2).[47]

Ischemic neuromyopathy of the pelvic limbs (aortic trifurcation embolism or classic saddle embolus) is described classically as paresis or paralysis with absence of segmental reflexes, firm and painful pelvic limb musculature, and cold and pulseless limbs with cyanotic nail beds (Figure 37-3). The changes can be bilateral and symmetrical, bilateral and asymmetrical, or unilateral depending upon the degree of obstruction and vascular response. Clinical signs develop acutely and can worsen but usually remain stagnant or improve over the next several days to 3 weeks. Improvement can be dramatically quick in some cases. This may represent the fracturing of a friable embolus or distal migration of the embolus. Many cats regain some to all motor function of the pelvic limbs within 4 to 6 weeks from the initial event because of establishment of a collateral network, recanalization through the embolus, or intrinsic dissolution of the embolus.[48] For these reasons, even though the recurrence rate for CE can be as high as 75 per cent,[49] owners should be encouraged to at least consider therapy and not to choose immediate euthanasia. More chronic complications from INM include self-mutilation, limb necrosis requiring amputation, and limb contracture.[9] Nuclear perfusion studies that use intravenous injection of free or unbound technetium 99m (^{99m}Tc) performed 48 to 72 hours after the CE event can help identify cats at risk for long-term ischemia, or document adequate collateral flow in those cats with continued neurological dysfunction (Figure 37-4).

The clinical signs associated with brachial embolism are essentially identical to those for embolism of the aortic trifurcation, although they are asymmetrical, with the right forelimb affected most commonly.[48]

In addition to the clinical signs associated with the infarcted vascular bed, respiratory signs (tachypnea, dyspnea), hypothermia, and cardiac auscultatory changes (murmur, gallops) are identified commonly. Concurrent congestive heart failure (CHF) is reported in 44 to 66 per cent of cases and can progress during acute management.[3,9,16] The most commonly encountered biochemical changes include elevation in muscle enzymes (AST, ALT, CK), hyperglycemia, azotemia, hypercholesterolemia, and hypocalcemia. Hyperkalemia is encountered occasionally and may develop during acute management.



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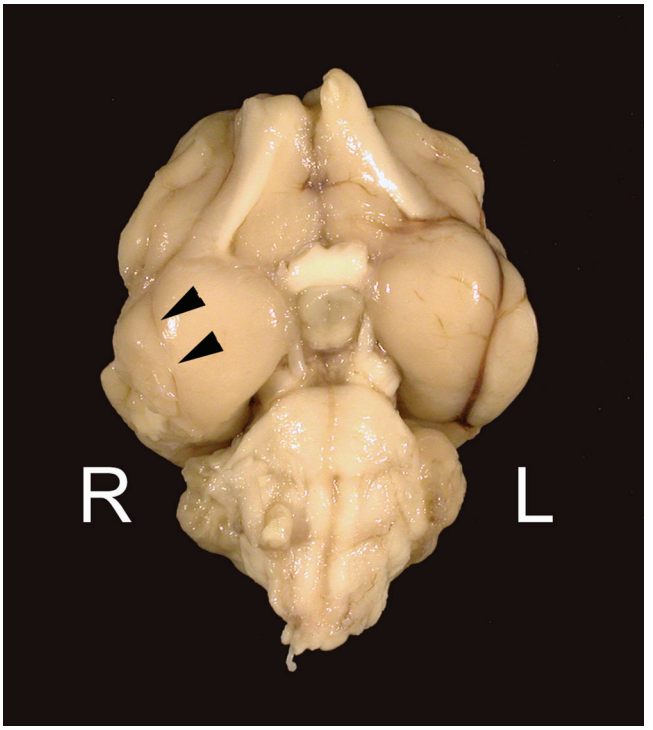
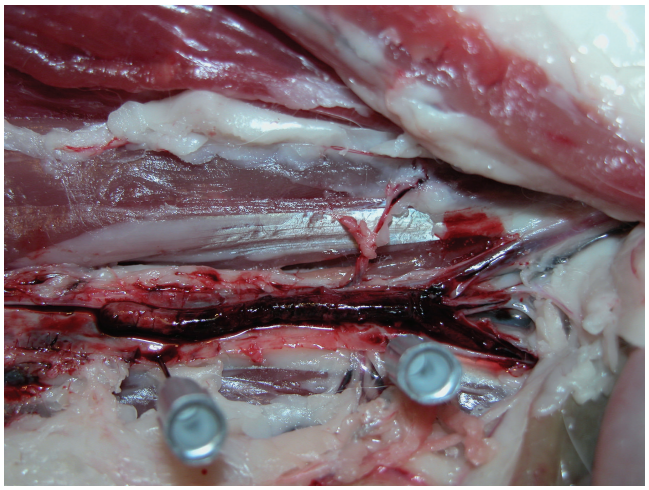


B

Figure 37-2. A, Large occlusive embolus within the right common carotid artery. **B,** Brain (ventral aspect) of the cat in Figure 37-2, *A*. Reduced vascularity along the right side of the brain *(arrowheads)* as a result of the embolism of the right common carotid artery.



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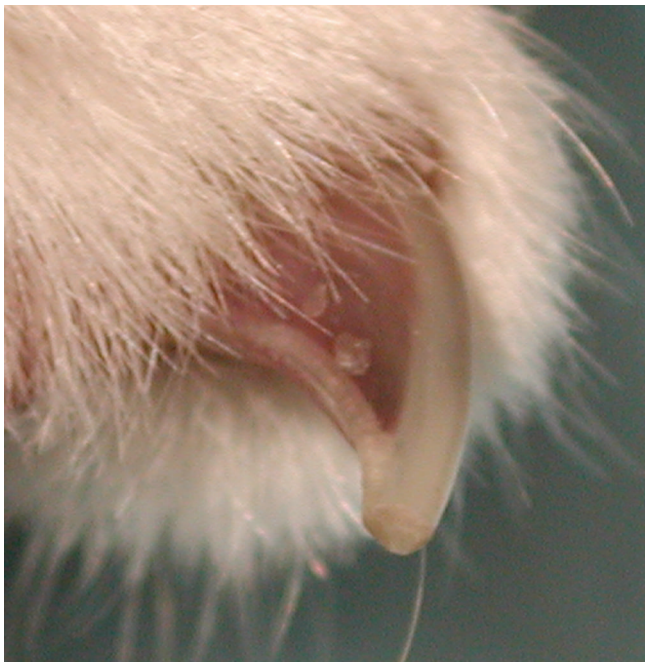

B

Figure 37-3. A, Large occlusive embolus can be seen at the aortic trifurcation. **B,** Cyanotic nail beds as a result of ischemia from an occlusive aortic trifurcation embolus.

Disturbances in coagulation parameters have been identified in some cats on presentation. Electrocardiography may suggest left ventricular enlargement and identify conduction abnormalities such as left-anterior fascicular block and supraventricular or ventricular arrhythmias.

MANAGEMENT

The focal points in the acute management of CE are to (1) reduce continued thrombus formation associated with the embolus, (2) improve blood flow (either aortic or collateral), (3) pain management, (4) treat concurrent congestive heart failure if present, and (5) provide supportive care.

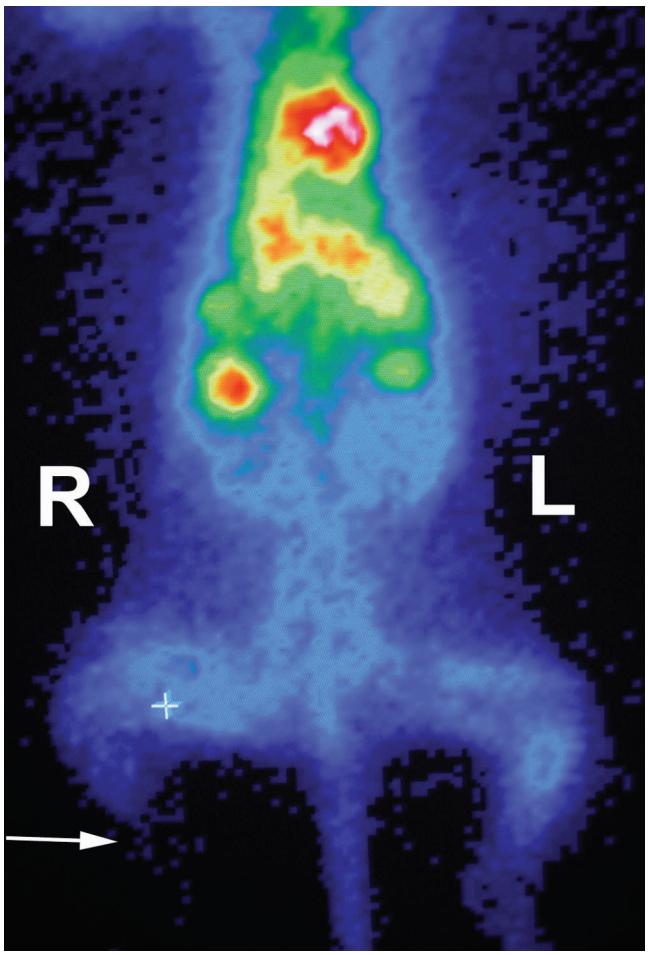

Figure 37-4. Nuclear perfusion study using free (unbound) technetium^{99m} (^{99m}Tc) demonstrating essentially no perfusion distal to the midtibial region *(arrow)* in the right hind limb of a cat approximately 48 hours after an aortic trifurcation embolization.

Reducing Thrombus Formation

Heparin

The most common agent chosen to reduce continued thrombus formation at the site of embolization is unfractionated heparin (UH). Unfractionated heparin inhibits the formation of the active form of factors X and II and therefore is classified as an anticoagulant. Unfractionated heparin also exhibits an antiplatelet effect in healthy human beings by binding to and inhibiting von Willebrand's factor (vWF).[50] However, human patients with diseases known to be associated with hypersensitive platelets, such as PAD, exhibit spontaneous aggregation in response to UH in addition to increased responses to physiological agonists.[51-53] This direct effect of heparin on platelets may be a cause of heparin-induced thrombosis and thrombocytopenia outside of classic immunological mechanisms. Ideally, a coagulation panel including platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) should be submitted as soon as the clinical suspicion of CE is high. This allows determination of baseline coagulation function before UH therapy and identification of those cats that may have a coagulopathy such as disseminated intravascular coagulation. Adequate dosing of UH in cats with

thromboembolic disease varies.[54] A prudent beginning dosing regimen is 250 to 375 IU/kg IV initially, followed by 150 to 250 IU/kg SQ q6-8h. Injections should be given cranial to the diaphragm to ensure adequate absorption. Although some investigators suggest the aPTT does not correlate well with plasma UH levels,[54] it is readily available to practitioners and should be used to adjust the UH dose to a target of 1.5 to 2.0 times the baseline value. Given the potential issue of heparin-induced platelet activation, concurrent administration of antiplatelet agents such as aspirin or clopidogrel (Plavix) (see section on prevention) could be considered but this has not been investigated clinically.

Low-Molecular-Weight Heparins

The low-molecular-weight heparins (LMWH) or fractionated heparins (FH) are an alternative to standard heparin or UH. These agents are smaller in size than UF but maintain a critical peptide sequence that prevents the activation of factor X and is discussed in more detail within the section on prevention. They have less activity towards factor II; therefore, monitoring of the aPTT is not required. Minimal antiplatelet effects occur in normal human beings when compared with UH[50]; however, these drugs do exhibit similar, although fewer, proaggregating effects in human patients with hypersensitive platelets.[51,52] The cost for these agents is considerably more expensive than UH (approximately $3 to $5 per dose) but can be administered subcutaneously only twice daily in human beings for acute management of unstable angina, non–Q-wave myocardial infarction, deep venous thrombosis, and pulmonary thromboembolism. Dalteparin (Fragmin) and enoxaparin (Lovenox) have been used in cats at 100 IU/kg SQ q24-12h and 1.0 to 1.5 mg/kg SQ q24-12h, respectively.[55,56] However, the effective dose required for adequate inhibition of factor Xa has not been determined in cats with CE.

Improvement of Arterial Blood Flow

Aortic Flow and Thrombolytic Therapy

Reestablishing arterial flow to the infarcted organs would appear to be a primary therapeutic goal. This could be accomplished by removal of the aortic embolus through either embolectomy or dissolution with use of thrombolytic drugs. Embolectomy is limited in cats, and surgical intervention is contraindicated given the operative risks. Thrombolytic drugs such as streptokinase[6,57] and tissue plasminogen activator (t-PA)[49] have been used in cats to dissolve emboli and reestablish aortic flow. Ideally, thrombolytics would be administered as soon as possible after the embolic event; however, effective dissolution has been noted as late as 18 hours after initial clinical signs.[58]

Severe adverse effects can be associated with thrombolytic therapy; therefore the use of these drugs should not be undertaken without some consideration. The sudden resumption of arterial flow to infarcted organs, especially the pelvic limbs, results in the mobilization of metabolic products such as potassium and organic acids from ischemic/necrotic tissues into the systemic circulation. This can result in life-threatening hyperkalemia and severe metabolic acidosis, which may require immediate and aggressive therapy. The frequency of hyperkalemia and reperfusion injury after embolus dissolution with thrombolytic therapy is 40 to 70 per cent.[6,49,57] Reperfusion injury represents the most common cause of death in cats that receive thrombolytics, with survival rates ranging from 0 to 43 per cent.[6,49,57] Cats with complete infarction such as bilateral paralysis appear more likely to develop hyperkalemia and metabolic acidosis. This probably is related to the larger area of ischemia.[6,49] Given that approximately 50 per cent of cats regain motor function over a 4-week to 6-week period after the CE event with conservative treatment,[48] the benefit-to-risk ratio for thrombolytic therapy must be determined for each individual cat. Although it would appear that cats with more complete infarction should not receive thrombolytic therapy because of higher risk for reperfusion injury, these cats probably are less likely to regain motor function with conservative therapy than those with a unilateral infarction; therefore, chances of recovery for cats with complete infarction may be improved with thrombolytic therapy .

Thrombolytic therapy is expensive and may be cost prohibitive to some owners. Because of potential adverse effects and cost, thrombolytic therapy should not be used in all cases of CE. However, thrombolytics should be strongly considered in cases of cerebral, splanchnic, or renal infarction because the reestablishment of arterial flow is paramount.

Streptokinase

Streptokinase combines with plasminogen to form an activator complex that converts plasminogen to the proteolytic enzyme plasmin. Plasmin degrades fibrin, fibrinogen, plasminogen, coagulation factors, and streptokinase. The streptokinase-plasminogen complex converts circulating and fibrin-bound plasminogen and therefore is considered a nonspecific activator of plasmin. This results in a systemic proteolytic state that may predispose to bleeding from loss of coagulation factors and increased fibrin-degradation products.

In one retrospective study, 65 per cent of cats developed abnormal coagulation parameters after beginning streptokinase therapy, although some of these cats also were receiving heparin.[6] Spontaneous bleeding from oral or rectal orifices or catheter sites was seen in 24 per cent of cats, including 36 per cent of the cats with abnormal coagulation parameters. Transfusions were required in 27 per cent of the bleeding cats, and only 18 per cent of these (transfused) cats survived streptokinase therapy. Increased respiratory rates have been seen in 30 per cent[6] and 50 per cent[57] of cats treated with streptokinase, although this was caused by worsening of congestive heart failure in the small number of cats examined (3 out of 14) from one study.[6] Hyperkalemia develops in approximately 40 per cent[6,57] of cats and is more likely to be seen with longer infusion periods, which may be related to more severe obstruction.[6]

Streptokinase has been shown to exhibit a clinical thrombolytic effect in one retrospective study.[6] Approximately 50 per cent of cats had a return of femoral pulses within 24 hours of initiation of streptokinase therapy. Motor function returned in 30 per cent, and 80 per cent of these cats regained motor function within 24 hours. Cats with single limb infarction did dramatically better: 100 per cent regained pulses and 80 per cent regained motor function. Of those cats that had infarction of both limbs, only about 50 per cent regained pulses, whereas approximately 25 per cent regained motor function. This would appear worse than the 50 per cent reported return of motor function for conservative therapy. However, this may be influenced by the fact that other retrospective studies may have had a

larger percentage of single limb infarctions, which are more likely to respond to conservative therapy. Although comparison of different retrospective studies is difficult at best, this may provide supportive evidence that thrombolytic therapy should be reserved for those cats with more complete infarction.

The survival data from the two retrospective studies evaluating streptokinase are different. In one study,[57] all of the cats died suddenly during the infusion period, whereas another study demonstrated an overall 33 per cent survival rate.[6] In the latter study, about 50 per cent of the cats that did not die in the hospital were euthanized because of complications or poor prognosis.

Streptokinase (Streptase, Aventis Behring, King of Prussia, PA) typically is administered by giving 90,000 IU IV over 1 hour, followed by an infusion of 45,000 IU per hour for up to 8 hours. Streptokinase potentially is antigenic, but allergic reactions have not been reported in cats. Currently the smallest amount of streptokinase that can be purchased is 750,000 IU (estimated cost of $300), which would provide more than 15 hours of infusion time. Once reconstituted, it must be used within 8 hours if stored at 2° to 8° C.

Tissue Plasminogen Activator

Unlike streptokinase, t-PA does not bind circulating plasminogen readily and therefore does not induce a systemic proteolytic state. Plasminogen and t-PA have a high affinity for fibrin, so they bind to thrombi/emboli in close proximity. This results in a relatively thrombus/embolus-specific conversion of plasminogen to plasmin. For these reasons, bleeding complications are considered less likely than with streptokinase. However, reperfusion injury can occur with t-PA as with streptokinase.

One clinical trial of t-PA in cats demonstrated a clinical thrombolytic effect.[58] Complications included minor hemorrhage from catheter sites (50 per cent), fever (33 per cent), and reperfusion injury (33 per cent). The acute survival rate was 50 per cent, with deaths attributable to reperfusion injury and cardiogenic shock. Of the cats that survived, 100 per cent had infarction of both limbs. Perfusion was restored within 36 hours and motor function returned within 48 hours in 100 per cent of surviving cats. These data indicate that t-PA therapy has a better outcome than streptokinase. However, this study was small (six cats) and may not be representative of the larger population.

The recommended dosing protocol for human recombinant t-PA (Activase, Genentech, San Francisco, CA) is 0.25 to 1 mg/kg/hr IV for a total dose of 1 to 10 mg/kg.[49] Activase is supplied in 50-mg and 100-mg bottles with an estimated cost of $1500 and $3000, respectively. The average cat does not require more than 50 mg, and smaller amounts of t-PA can be purchased (Cathflo Activase, Genentech, San Francisco, CA) for approximately $100 per 2 mg. This may be more cost effective for small cats or allow owners who have budget constraints to attempt the low end of the dosage range. For example, a typical cat weighing 4.5 kg could receive 2.2 mg/kg for about $500. The concentration of t-PA is 1 mg/ml when reconstituted and is active for up to 8 hours when stored at 2° to 8° C.Tissue plasminogen activator has been frozen in a regular freezer (–20°C) for up to 6 months without losing thrombolytic activity in an *in vitro* cat whole-blood thrombus model.[59] This may allow unused portions of the drug to be administered to cats at a later time. However, it contains no preservatives, so sterility cannot be guaranteed.

Improvement of Collateral Flow

If dissolution of the embolus is unsuccessful or not attempted, increasing perfusion to the pelvic limbs can be attempted by enhancing flow through the collateral network. Historically, acepromazine, an α_1 receptor blocker, has been used to dilate the collateral vessels and improve perfusion. There is no evidence that vasodilatation occurs, and hypotension may result, which actually reduces perfusion; therefore acepromazine is no longer indicated.

As mentioned in the section on pathogenesis, loss of aortic flow alone does not result in clinical signs of INM. However, platelet release products (serotonin and/or thromboxane) have been implicated as the agents responsible for loss of collateral flow associated with aortic trifurcation embolism. Therefore antiplatelet agents may help improve collateral flow by reducing the amount of vasoactive substances released from platelets. For these agents to be most helpful, they should be given as soon as possible after the CE event. These agents are discussed in detail in the prevention section; however, their properties related to effects on collateral flow are presented here.

Aspirin

Aspirin has been shown to reduce the amount of released thromboxane A_2 from activated cat platelets and to improve collateral flow in an experimental cat model of aortic trifurcation embolism.[44,45] In the latter study,[45] 650 mg (approximately 150 mg/kg) of aspirin given orally 1 hour before thrombus formation resulted in plasma salicylate levels of 200 to 300 µg/ml and was considered representative of therapeutic concentrations. However, salicylate toxicity in cats has been documented at plasma levels of 300 µg/ml.[60] The cats were sacrificed within 4 hours, so clinical signs of toxicity may not have been apparent within such a short period. Given that antiplatelet effects can be seen at 20 to 50 µg/ml and this can be accomplished with a dose of 10.5 mg/kg in cats,[61] administration of no more than the standard dose of 25 mg/kg of aspirin would seem prudent to avoid potential toxicity. However, the effect of aspirin on collateral flow has been documented only at the 650-mg dose.

Clopidogrel (Plavix)

Clopidogrel (Plavix) has been shown to reduce serotonin release from activated platelets in cats, whereas studies in other species have demonstrated reduced production of thromboxane.[62,63] Evidence also exists that clopidogrel and the related compound ticlopidine act as vasomodulating agents in rats, rabbits, and dogs in which vasoconstriction of arterial ring preparations in response to serotonin, endothelin, and arachidonic acid is reduced.[64,65] This vasomodulating effect may be responsible at least partially for reduced ischemic damage seen in experimental models of ischemic stroke.[66,67] In human beings, the onset of action for clopidogrel is 2 hours; however, maximal effects are not achieved until 3 to 5 days of daily administration.[68,69] To hasten the pharmacological effect, an oral loading dose of 300 mg (four times the daily dose of 75 mg) exhibits antithrombotic effects within 90 minutes and has been implemented for acute ischemic events and vascular interventions.[70-72] In cats, maximal antithrombotic effects are

achieved within 72 hours of daily administration of 18.75 mg.[62] Daily administration of 75 mg in cats (four times 18.75 mg) is well tolerated and not associated with adverse effects. Therefore, although no objective data support this assertion, the administration of 75 mg of clopidogrel orally upon presentation may be helpful in improving collateral flow and should not be associated with adverse effects or toxicity.

Pain Management

Cardiogenic embolism can result in severe pain, and controlling this pain is a vital aspect of acute CE treatment. While some cats may demonstrate clear and dramatic signs such as vocalization and self-mutilation, others patients may be more stoic and only exhibit anorexia, elevated heart rate, or mild anxiety. It should be assumed that all cats are experiencing clinically relevant pain and analgesics should be considered. Narcotics work very well and are the agents used most commonly. Acepromazine is a sedative but does not have analgesic properties. Butorphenol tartrate (0.2 to 0.4 mg/kg SQ, IM, IV q1-4h), hydromorphone (0.08 to 0.3 mg/kg SQ, IM, IV q2-6h), buprenorphine HCL (0.005 to 0.01 mg/kg SQ, IM, IV q6-12h), and oxymorphone HCL (0.05 to 0.1 mg/kg SQ, IM, IV q1-3h) have been used widely in cats and appear to provide good analgesia with few adverse effects.[73] In severe or refractory cases, fentanyl citrate (4 to 10 µg/kg IV bolus followed by 4 to 10 µg/kg/hr infusion) can be used.[73] Injections should be given cranial to the diaphragm to ensure adequate absorption.

Treatment of Concurrent Congestive Heart Failure

Decompensated congestive heart failure is a common comorbid condition associated with CE and is reported in 44 to 66 per cent of cases.[3,6,9,16] Acute management with diuretics, oxygen, and nitroglycerin is important and frequently results in resolution of the congestive state. The reader is directed to more detailed sources for review of treatment options (see Chapter 34).

Supportive Care

The overall health of the cat must be kept in mind during the acute treatment for the CE event. Nutritional support is a critically important aspect that often is overlooked (see Chapter 16). If the cat is not eating or the caloric intake is inadequate, nasoesophageal feeding should be considered. Hypothermia commonly is associated with CE and INM, which most likely is related to reduced perfusion and therefore decreased rectal temperature. Historically, application of heating pads or other external heat sources has been encouraged, but this could result in thermal injury to the infarcted tissues and should be avoided. However, blankets or increased air temperature are acceptable.

Fluid therapy may be necessary in hypotensive cats and may assist in the removal of metabolic toxins such as potassium and organic acids released from infarcted tissues in addition to vasoactive substances released from activated platelets. On the other hand, many cats are in congestive heart failure when they are presented, and many more are likely to decompensate if fluid therapy is too aggressive. Therefore use of parenteral fluid therapy cautiously is recommended only in cases that would benefit from its use. Physical therapy to maintain flexibility of joints and encourage collateral flow is encouraged but may have to be postponed until the initial painful period has subsided.

SURVIVAL

The reported survival rates for initial CE events are remarkably similar, whether conservative (35 to 39 per cent)[3,9,16] or thrombolytic (33 per cent)[6] therapy is used. Cats with single pelvic limb infarction do dramatically better (68 to 93 per cent survival)[3,6,9,16] than do cats with bilateral pelvic limb infarction (15 to 36 per cent survival), regardless of therapy used.[3,6,9,16] Nonsurvival rates range from 61 to 67 per cent, with natural death rates (28 to 40 per cent) similar to euthanasia rates (25 to 35 per cent).[3,6,9,16] Nonsurvival has been associated significantly with hypothermia,[6,9] reduced heart rate,[9] and absence of motor function.[9] Reported long-term median survival times after the initial CE event have ranged from 51 days to 345 days.*

PREVENTION

Primary prevention of CE is defined as preventing the first CE event in a cat at risk for the disease. As mentioned previously, the incidence of CE in cats without a previous episode ranges from 5 to 17 per cent,[7,15] and given the relatively low survival rate from an initial CE event (approximately 36 per cent), primary prevention would be an ideal and logical goal. However, no such study has been performed in veterinary medicine; therefore no therapeutic recommendations can be made with any scientific support. Unfortunately, such a study probably will never be performed given the limitations of population size, length of required study period, nonstandardization of cardiac therapy, and cost. However, a large retrospective study of hypertrophic cardiomyopathic cats demonstrated that patients with CE had a significantly larger left atrial size than asymptomatic cats or cats with congestive heart failure.[7] These cats also had significantly larger end-systolic left ventricular dimensions (LVIDs) and lower fractional shortening (%FS). Similar patterns have been seen in human beings. These findings, combined with clinical experience, have led to the recommendation that prophylactic antithrombotic therapy be considered in cats with echocardiographic measurements of end-systolic left atrial diameters (LAs) greater than 1.7 cm or left atrium-to-aortic ratios (LA/Ao) greater than 2.0.[74] Prophylactic antithrombotic therapy also is indicated in cats with spontaneous contrast or "smoke" in the left atrium on echocardiography.[74]

Secondary prevention has received more attention in veterinary medicine and is defined as preventing a subsequent CE event in a cat that has a history of CE. However, this information is based on retrospective, non–placebo-controlled studies of individual antithrombotic agents. Therefore, no scientific basis exists for saying that any antithrombotic agent is effective for secondary prevention of CE in cats or that any one agent is more effective than another. With this is mind, the recurrence rate for CE in a very small number of cats (five) not receiving antithrombotic therapy was 40 per cent with a 1-year recurrence rate of 25 per cent.[16] Reported recurrence rates for cats receiving an antithrombotic drug range from 17 to 75 per

*References 3,4,6,7,9,16.

cent[3,6,9,16,49] with a 1-year recurrence rate of 25 to 50 per cent.[6,16] The term "recurrence rate" constitutes the overall recurrence rate over the entire life of the cats or at some nonuniform point after the initial CE event. It may be more appropriate to express recurrence rates over uniform points such as 3, 6, or 12 months post initial CE event. This also may allow better risk assessments to be determined and to be applied to a larger population.

Many of the studies focused on median survival time, which compromises the antithrombotic drug effect because many cats die from congestive heart failure, are euthanized because of poor quality of life issues, or die or are euthanized from other non-CE events. This effect can be dramatic considering that as many as 40 per cent of cats in the studies are dead from non-CE events within the first 30 days after the initial CE event.[6,16] Perhaps it would be more appropriate if survival statistics in such studies focused on vascular death or death/euthanasia directly attributable to CE. Designing and completing a prospective, comparative antithrombotic trial for secondary CE prevention is more practical than a primary prevention study because of high recurrence rates and relatively short study period. Hopefully, such a study can be accomplished in the near future.

Treatment of Underlying Myocardial Disease

The best way to prevent a CE event is to reverse the underlying myocardial disease and remove the medium for thrombus formation. Unfortunately, only taurine-deficient dilated cardiomyopathy appears reversible, and this accounts for a minority of cardiomyopathic cases now that taurine is supplemented routinely in commercial diets. However, appropriate therapy for underlying cardiac disease can result in improved cardiac function, which can lead to reduced ventricular filling pressures and left atrial dilatation, which therefore reduces the risk for thrombus formation. The reader is directed to other detailed sources for current therapeutic recommendations for cardiac disease in cats (see Chapter 34).

Antithrombotic Drugs

Because the underlying cardiac disease can be reversed only rarely, antithrombotic agents have become a mainstay for the primary and secondary prevention of CE. The two major categories of antithrombotics are antiplatelet agents and anticoagulants.

Antiplatelet Agents

These agents inhibit some aspect of platelet adhesion, aggregation, or release reaction and impair the formation of the initial platelet-rich thrombus at the injured endothelial site. Some of these agents also exhibit some vasomodulating effects by interfering with vasoactive substances such as serotonin and thromboxane A_2. These drugs have been used extensively for arterial thrombosis, and in specific circumstances for cardiogenic embolism in human patients.

ASPIRIN. Aspirin is the most used and studied antiplatelet agent available today. It acetylates platelet cyclo-oxygenase irreversibly, preventing the formation of thromboxane A_2, which has potent proaggregating and vasoconstrictive properties (Figure 37-5). Because the platelet has to be activated before thromboxane production, aspirin is considered a modest and indirect antiplatelet agent that inhibits secondary (aggregation induced by platelet-release products) but not primary platelet aggregation. Platelets are anuclear and are unable to synthesize new cyclo-oxygenase, so they are inhibited for their lifespan. Aspirin also acetylates cyclo-oxygenase irreversibly within endothelial cells, in which prostacyclin, which exhibits antiaggregating and vasodilating properties, is the end product. Endothelial cells, however, contain nuclei and are able to overcome this inhibition, so antithrombotic properties predominate in the clinical setting.

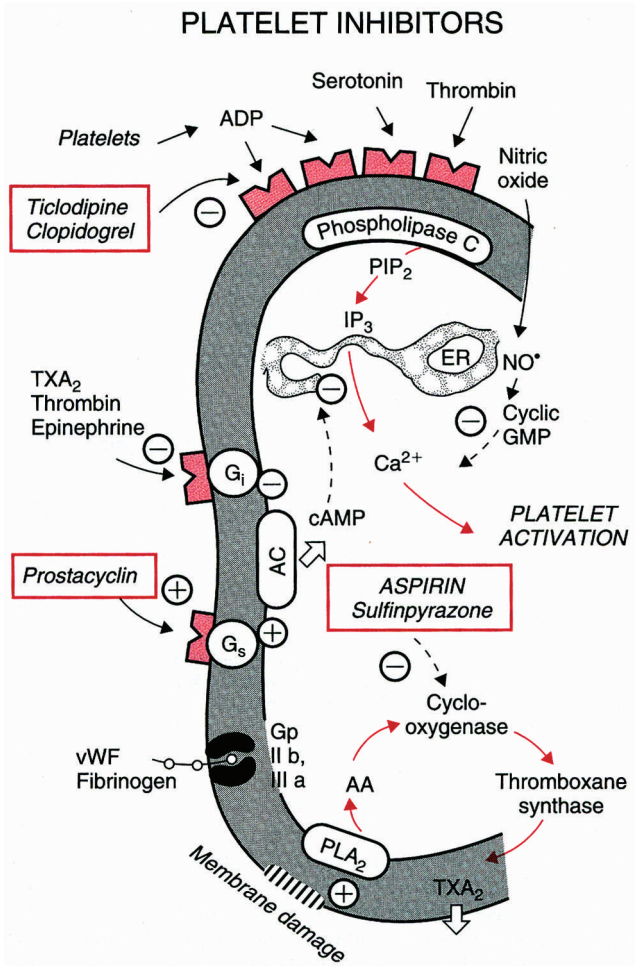

Figure 37-5. Mechanisms of action of the antiplatelet agents aspirin, ticlopidine, and clopidogrel. (*ADP,* adenosine diphosphate; *PIP_2,* phosphatidylinositol diphosphate; *IP_3,* inositol triphosphate; *ER,* endoplasmic reticulum; *cGMP,* cyclic guanosine monophosphate; *TXA_2,* thromboxane A_2; *G_i,* inhibitory G protein; *AC,* adenyl cyclase; *G_s,* stimulatory G protein; *cAMP,* cyclic adenosine monophosphate; *vWF,* von Willebrand factor; *Gp IIb,IIIa,* glycoprotein IIb/IIIa receptor complex; *PLA_2,* phospholipase A_2; *AA,* arachidonic acid.) (From White HD, Gersh BJ, Opie LH: Antithrombotic agents: platelet inhibitors, anticoagulants, and fibrinolytics. In Opie LH, Gersh, editors: Drugs for the heart, ed 5. Philadelphia, 2001, WB Saunders, p. 278.)

The prophylactic effect of aspirin on arterial thrombosis in human beings is well established. One extremely large meta-analysis of 140,000 patients in 300 studies demonstrated reduced death, myocardial infarction, and stroke in patients with various cardiovascular conditions.[75] However, a prophylactic effect on CE is much less demonstrable. Atrial fibrillation from multiple causes is the most common cause of CE in

human beings and has received extensive study. Aspirin has been shown to provide benefit comparable to warfarin in primary prevention in low-risk patients (normal systolic function) in some studies,[76,77] whereas other investigators have demonstrated no benefit[78] or reduced benefit compared to warfarin.[79] The general opinion of the medical community is that warfarin is about twice as effective as aspirin in primary prevention of CE with atrial fibrillation. However, some investigators argue that the overall low incidence for CE in low-risk patients, combined with the small real clinical advantage of warfarin, is overcome by the increased risk for bleeding, especially in the elderly, making aspirin the more logical choice.[80]

With respect to secondary prevention, aspirin appears to be inferior to warfarin[81,82]; however, no controlled antithrombotic trial has been performed in patients with underlying cardiomyopathy in whom atrial fibrillation is not present. In data subset analysis from large heart failure trials, mixed results demonstrate significant reduction in CE events with aspirin in one study[83] but not in another.[84] In both studies, however, antithrombotic therapy was associated with a more favorable outcome, with warfarin performing better than aspirin. The presence of atrial fibrillation, intracavitary thrombus, or previous CE event was considered a definite indication for warfarin therapy.

Aspirin generally is well tolerated by human beings; however, gastrointestinal adverse effects can be seen in up to 40 per cent of patients on standard doses. Gastrointestinal bleeding including melena and hematemesis occurs much less commonly. The use of very low–dose aspirin reduces the bleeding risk dramatically but results in almost no change in gastrointestinal upset.[85]

The pharmacological, analgesic, and antiplatelet effects of aspirin have been well studied in cats. Aspirin has only been shown to inhibit platelet aggregation consistently in response to arachidonic acid.[86,87] One study using whole-blood aggregometry was unable to demonstrate any inhibitory effect of aspirin on collagen-induced aggregation,[87] whereas another study identified a significant inhibition when using platelet-rich plasma.[88] Both studies used similar dosages (approximately 81 mg per cat), but the former study used a dosing interval of 72 hours, whereas the latter dosed every 48 hours. Two different studies were unable to demonstrate a significant inhibitory effect of aspirin on ADP-induced platelet aggregation,[87,88] although this was noted in another study using a very high dose of aspirin (625 mg).[44] In this latter study, blood was collected after major surgical intervention and thrombus formation with the administration of thromboplastin, which may have resulted in platelet exhaustion and an inability to respond to agonists. Cats that underwent surgical intervention and thrombus formation without aspirin therapy were not studied, so a definitive aspirin effect cannot be determined.

Aspirin has been used for primary and secondary prevention of CE in cats for more than 30 years. Recurrence rates from retrospective studies range from 17 to 75 per cent.[3,9,16,49] The standard dose for aspirin has been 25 mg/kg PO q72-48h. This works out to approximately 81 mg/cat or 1 low-dose adult aspirin. Adverse effects typically are gastrointestinal, such as anorexia and vomiting, and have been reported in up to 22 per cent of treated cats.[9] Published median survival times after a CE event have ranged from 117 to 180 days.[9,16] Recently, some consideration has been given to use of a lower dose of aspirin for the prevention of CE. The underlying theory is that higher doses, such as 25 mg/kg, induce enough inhibition of endothelial cyclo-oxygenase that levels of beneficial prostacyclin are reduced, thereby masking a more pronounced beneficial aspirin effect. One study has compared a low-dose aspirin protocol (5 mg/cat PO q72h) retrospectively with higher aspirin dosages.[9] There was no significant difference in recurrence rate or median survival time; however, the rate of adverse gastrointestinal events was reduced.

The cost of standard aspirin therapy is extremely low ($0.15 to $0.25 per month) and requires no monitoring. The use of low-dose aspirin requires compounding and increases the cost to approximately $15 to $20 per month, thereby losing the cost benefit of this drug. If a lower dose is desirable to avoid adverse gastrointestinal events, then consider using one fourth of an adult low-strength tablet (20.25 mg) PO q72-48h ($0.04 to $0.07 per month).

THIENOPYRIDINES. This class of drugs induces specific and irreversible antagonism of the ADP_{2Y12} receptor along the platelet membrane (see Figure 37-5). These agents are considered direct antiplatelet agents and inhibit primary and secondary platelet aggregation in response to multiple agonists and prolong mucosal bleeding times.[89-92] The antiplatelet effects are more potent than those induced by aspirin. The ADP-induced conformational change of the glycoprotein IIb/IIIa complex also is inhibited, which reduces binding of fibrinogen and von Willebrand factor (see Figure 37-5).[90,93] These agents also impair the platelet release reaction, decreasing the release of proaggregating and vasoconstrictive agents such as serotonin, ADP, and thromboxane.[62,63,94,95] Vasomodulating effects also have been seen through in vitro studies.[64,65]

The two drugs in this class include ticlopidine (Ticlid) and clopidogrel (Plavix). Neither of these parent compounds possesses antiplatelet effects, instead they must undergo hepatic biotransformation to form at least one active metabolite.[96-98] These drugs have been shown to be more effective than aspirin in arterial thrombosis by decreasing stroke, myocardial infarction, or vascular death.[99-101] There have been no clinical studies reporting their effectiveness in primary or secondary prevention of CE, probably related to the inferior performance of aspirin compared to warfarin. However, such studies are now ongoing.

Ticlopidine (Ticlid). This was the first drug of this class used in human beings. Onset of action is delayed within 2 to 4 days, with maximal effects reached between 4 and 6 days of drug administration. Antiplatelet effects are lost between 4 and 8 days after discontinuation of drug administration.[102] Adverse events are a limiting factor and include gastrointestinal disturbances (nausea and diarrhea), dermatological problems (maculopapular or urticarial rashes), rare bleeding, agranulocytosis, hepatic problems (cholestatic jaundice), and thrombotic thrombocytopenic purpura (TTP).[89,103,104] A short-term pharmacodynamic study in normal cats demonstrated consistent antiplatelet effects, including reduced platelet aggregation in response to ADP and collagen, prolonged oral mucosal bleeding time, and reduced serotonin release when dosed at 250 mg/cat PO twice a day.[95] However, the majority of cats demonstrated dramatic gastrointestinal adverse effects, including anorexia and vomiting at this dose, precluding its clinical usefulness. Clopidogrel has supplanted ticlopidine in human medicine because of its equal or better clinical efficacy and more favorable safety profile.

Clopidogrel (Plavix). Clopidogrel is a second-generation thienopyridine that is more potent than ticlopidine. Similar to ticlopidine, maximal effects are not achieved until 3 to 5 days of daily administration, and antiplatelet effects are lost between 5 and 7 days after discontinuation of drug administration in human patients.[68,69] Adverse effects are less common than ticlopidine in human beings and include gastrointestinal (gastric upset, diarrhea) dermatological problems (pruritus, rash) and occasional minor bleeding.[105] Agranulocytosis and TTP were not identified in the largest clinical trial of clopidogrel (CAPRIE trial).[101] However, cases of clopidogrel-associated TTP have been reported after completion of the CAPRIE trial, although the incidence appears to be similar to that for the general population.[106] In the CAPRIE trial, only diarrhea and rash were more common with clopidogrel than that seen with aspirin, although overall gastrointestinal adverse effects, including bleeding, were significantly less with clopidogrel.[105]

In a short-term pharmacodynamic study in normal cats, clopidogrel was shown to induce a 95 per cent inhibition in platelet aggregation in response to ADP, 92 per cent inhibition in serotonin release, and a 3.9-fold prolongation in oral mucosal bleeding time when dosed at 18.75 mg, 37.5 mg, and 75 mg PO q24h.[62] The maximal antiplatelet effects were seen by 3 days of drug administration and were lost within 7 days after drug discontinuation. No adverse effects were noted during this study, or in approximately 30 clinical cats that have received daily clopidogrel over an 18-month period.[108] All three dosages had equipotent antiplatelet effects, so using the lowest dose (18.75 mg PO q24h) appears a reasonable starting dose. A minimal effective dose was not established in this study nor was clinical efficacy for CE.

Clopidogrel is supplied as 75-mg tablets that cost approximately $4 each, which translates into approximately $30/month for a cat when dosed at 18.75 mg PO q24h. Given that clopidogrel is more potent than aspirin and has not been associated with adverse effects to date, it would appear to be a potentially viable alternative to aspirin therapy. Although the cost is considerably more than that for standard aspirin therapy, it is comparable to low-dose aspirin therapy.

Anticoagulants

This group of drugs inhibits the coagulation cascade by interfering with the formation of one or more active coagulation factors. Some of these drugs also exhibit relatively minor antiplatelet effects. These drugs are used in the acute management of stroke and myocardial function in addition to being the primary choice for primary and secondary prevention of CE and deep venous thrombosis in human patients.

WARFARIN. Warfarin inhibits the formation of the vitamin K–dependent coagulation factors II, VII, IX, and X, in addition to the anticoagulant proteins C and S. After warfarin administration in human patients, the levels of protein C fall before the coagulation factors, which results in a theoretical hypercoagulable state for 4 to 6 days. For this reason, unfractionated heparin or low-molecular-weight heparins are administered during this period. Whether such a hypercoagulable period exists in cats is unknown but it would be prudent to follow a similar treatment protocol. As mentioned previously, atrial fibrillation is the most common cause of CE in human beings and warfarin is considered the drug of choice for most patients. This is especially true for patients identified as high risk, which is defined as those persons who have left ventricular systolic dysfunction, intracavitary thrombus, or a previous episode of CE. Numerous studies have demonstrated the efficacy of warfarin for primary and secondary prevention of CE with atrial fibrillation, even when lower intensity anticoagulation protocols are used.* Similar to aspirin, warfarin was associated with fewer CE events from DCM in one study[83] but not another.[84] However, warfarin was associated with a significantly more favorable outcome in both studies. Bleeding is the most common complication in human beings, with clinical trials reporting a 1.3 to 2.5 per cent occurrence rate for major bleeding (fatal or life-threatening) and 16 to 21 per cent for minor bleeding.† This translates into an annual occurrence rate of 1.7 to 4.2 per cent, with a higher frequency in elderly patients. One study found a cumulative rate of bleeding of more than 40 per cent over a 3-year period.[111]

Warfarin has numerous interactions with other medications that may increase or decrease the anticoagulation effect, and these should be explored before beginning warfarin therapy or adding medications to a stable warfarin protocol. Warfarin therapy is adjusted to obtain a desired degree of anticoagulation. This is accomplished by monitoring the International Normalized Ratio (INR). The INR is considered superior to prothrombin time (PT) because the former is normalized for different thromboplastin reagents used in different laboratories by the equation ([patients PT/control PT]^{ISI}), in which ISI is the international sensitivity index for the thromboplastin. Medium anticoagulation intensity (INR of 2 to 3) is recommended for the prevention of CE in human patients. A standard protocol for monitoring INR in human beings is daily for the first 5 days, then three times weekly for up to 2 weeks. Once the steady-state warfarin dose is determined, the INR is measured every 4 to 6 weeks unless concurrent medications change.

The use of warfarin to prevent CE in cats was explored because many clinicians felt that the recurrence rates with aspirin were unacceptably high. Pharmacokinetic studies of warfarin in cats demonstrate that absorption after oral administration is rapid and undergoes enterohepatic recirculation, which may contribute to the known wide interindividual and intraindividual variable anticoagulant response.[112] Although unsubstantiated, a goal of PT prolongation of 1.3 to 1.6 times baseline or an INR of 2 to 3 has been considered as adequate anticoagulation. The published CE recurrence rates for cats receiving warfarin range from 42 to 53 per cent, with estimated mean survival times from 210 to 471 days.[3,6,74] Bleeding (both major and minor) is the most common complication seen in 13 to 20 per cent of cats, with fatal hemorrhage reported in up to 13 per cent of cats.[3,6,56,74]

The suggested starting dose for warfarin is 0.25 mg to 0.5 mg per cat PO q24h. Pharmacokinetic and pharmacodynamic data in cats suggest a starting dose of 0.06 mg/kg to 0.09 mg/kg PO q24h, which is within the 0.25 mg to 0.5 mg dose range for the average cat.[112,113] Concurrent heparin should be administered for at least 2 to 5 days after beginning warfarin therapy. Warfarin is not distributed evenly throughout the tablet, so given that most cats receive less than 1 mg (currently the smallest available tablet size), the tablet should be crushed and compounded by a pharmacist. Because of the wide

*References 76-79,81,82,106-110.
†References 76-79,81-82,109,110.

interindividual and intraindividual variation in anticoagulation response, close and careful monitoring is required, and owners should be aware of this commitment before beginning therapy because it requires dedication and increased expense for the owner.

Cats on warfarin therapy should be kept indoors to reduce the risk of trauma and potentially fatal hemorrhage. The recommended protocol for monitoring the INR or PT is daily for 5 to 7 days, then at least twice weekly for 2 to 3 weeks, once weekly for 2 months, and then at least once every 6 to 8 weeks. Adjustments to warfarin dosing based on chronic monitoring should involve changing the total weekly dose and not daily dose. The latter may result in too dramatic of a change in anticoagulation intensity and predispose to bleeding or thrombosis. A suggested protocol is presented in Table 37-1. With an INR greater than 5, vitamin K should be given at 1 to 2 mg/kg/day PO or SQ, and the INR monitored daily until it is less than 3. If severe blood loss has occurred, a whole blood transfusion should be considered in addition to subcutaneous vitamin K. The cost of warfarin is relatively cheap, but compounding increases the expense to approximately $15 to $25 per month.

LOW-MOLECULAR-WEIGHT HEPARINS. As mentioned previously, the low-molecular-weight heparins (LMWH) are smaller in size than standard heparin but maintain a critical peptide sequence that prevents the activation of factor X. They inhibit the activation of thrombin (IIa) to a lesser degree and are frequently expressed as anti-Xa:anti-IIa activity ratios. For example, the two most commonly used agents, dalteparin (Fragmin) and enoxaparin (Lovenox), have 2:1 and 3:1 ratios, respectively.[114] Because these agents have less inhibition of IIa, the PT will not prolong appreciably; instead anti-Xa activity is monitored. In human beings, the LMWH have a higher bioavailability and longer plasma half-life than standard heparin, allowing once or twice daily administration. As mentioned previously for the LMWH, they exhibit minimal antiplatelet effects when compared with UH.[50] They do exhibit proaggregating effects in human patients with hypersensitive platelets, although these are less than those seen with UH.[51,52]

Numerous studies in human beings have demonstrated that the efficacy of the LMWH is at least equal to UH, and better than placebo, with unstable angina and non–Q-wave infarction in the acute period.[115-118] After the acute period, the clinical effect did not appear to be better than aspirin.[115-118] The LMWH also have been shown to have efficacy at least equal to UH and better than warfarin or placebo, in the acute management (30 days or less) or perioperative prevention of deep venous thrombosis and pulmonary embolism in human patients.[119-123] Although no study has evaluated the efficacy of the LMWH on CE, one study did demonstrate a significantly reduced risk of left ventricular thrombus formation after acute myocardial infarction in human patients when treated with dalteparin during the hospital stay.[124] As with UH, the most common adverse effect of the LMWH is bleeding, with the frequency of minor bleeding reported from 5 to 27 per cent, and major bleeding from 0 to 6.5 per cent, which is similar to the occurrence seen with UH.[116-121,124] This group of drugs has not been used chronically in human beings because of the high cost for such long-term treatment and concerns about compliance because these drugs must be administered subcutaneously.

The LMWH have generated considerable interest in the prevention of CE in cats because of the positive studies and lack of monitoring in human patients. There has been one published pharmacokinetic study evaluating dalteparin in normal cats.[55] It demonstrated that when dosed at 100 IU/kg SQ q24h for 5 days, the anti-Xa activity achieved at 4 hours after administration was within the range considered therapeutic for human beings. However, one cat was followed longer than the 4-hour period and demonstrated that the anti-Xa activity level fell below the therapeutic range between 4 and 8 hours after administration. A recent abstract was presented that monitored anti-Xa levels in 5 normal cats that received Fragmin (100 IU/kg SQ q12h) or enoxaparin (1 mg/kg SQ q12h) for 5 days. While peak anti-Xa levels were reached at 4 hours, most of the cats never achieved levels considered therapeutic for human beings and the levels returned to baseline by 8 hours.[125] From these studies, it appears that cats at risk for CE, or those that have experienced CE, would require dosing at least every 8 hours. However, therapeutic anti-Xa levels have not been determined in normal cats, cats at risk for CE, or those that have experienced CE. There is also concern that cats with acute CE may have even less response to the LMWH. Additionally, the correlation between anti-Xa levels and thrombosis prevention in human beings is not strong, suggesting beneficial effects of the LMWH aside from their anti-Xa activity.[126-128] Anti-Xa activity assays can be run commercially through the Cornell University comparative coagulation laboratory (http://diaglab.vet.cornell.edu/coag).

One retrospective study comparing dalteparin to warfarin did not demonstrate a significant difference in CE recurrence rate (43 per cent vs. 24 per cent, respectively) or median survival time (255 days vs. 69 days).[56] However, this may have been influenced by a greater proportion of warfarin-treated cats dying early, with a few very long survivors, whereas the dalteparin group tended to have a more gradual and linear rate of death. This situation results in fewer cats receiving warfarin that are able to have a CE event. None of the cats receiving dalteparin experienced any bleeding complications.

Table 37-1 | **Total Weekly Dose (TWD) Adjustment of Warfarin Based on INR**

INR VALUE	ADJUSTMENT TO DOSE
1.0-1.4	↑ 10%-20% TWD Repeat INR in 1 week
1.5-1.9	↑ 5%-10% TWD Repeat INR in 2 weeks
2.0-3.0	No change Repeat INR in 6-8 weeks
3.1-4.0	↓ 5%-10% TWD Repeat INR in 2 weeks
4.1-5.0	DC warfarin 1 day ↓ 10%-20% TWD Repeat INR in 1 week
>5.0	DC warfarin until INR<3.0* Administer vitamin K until INR<3.0* ↓ 20%-40% TWD
IF DOSING 0.5 MG/CAT PO Q24H	
0.75 mg Wed	↑ 7% TWD
0.75 mg Tu/Thurs	↑ 14% TWD
0.75 mg Mon/Wed/Fri	↑ 21% TWD
0.25 mg Wed	↓ 8% TWD
0.25 mg Mon/Wed/Fri	↓ 27% TWD
0.25 mg Mon-Fri	↓ 55% TWD

*Monitor INR daily until <3.0.
Modified from Colorado State University canine protocol.
INR, International Normalized Ratio. *DC,* discontinue.

Table 37-2 | **Dosages for Suggested Antithrombotic Drugs**

PRIMARY PREVENTION	
Clopidogrel (Plavix)	18.75 mg/cat PO q24h
Aspirin	25 mg/kg PO q72-48h 5 mg/cat PO q72-48h (low-dose)
SECONDARY PREVENTION	
Clopidogrel (Plavix)	18.75 mg/cat PO q24h
Dalteparin (Fragmin)	100 IU/kg SQ q24-12h
Enoxaparin (Lovenox)	1.0-1.5 mg/kg SQ q24-12h
Aspirin	25 mg/kg PO q72-48h 5 mg/cat PO q72-48 h (low-dose)
Warfarin	0.25-0.5 mg/cat PO q24h

Currently, the recommended dosing protocols are 100 IU/kg SQ q24-12h for dalteparin and 1.0 to 1.5 mg/kg SQ q24-12h for enoxaparin. Again, based on pharmacokinetic data, the dosing frequency may be inadequate at once or twice daily. The estimated cost for once daily dalteparin is $80/month if the 9.5-ml, 10,000 IU/ml multidose vial is used, whereas the cost is greater if the single-dose syringes are used. Enoxaprin is more expensive, with an estimated cost of $160/month when dosed once daily.

Current Antithrombotic Recommendations (Table 37-2)

These recommendations are based on reviews of the current data from retrospective studies in veterinary medicine, comparative data from human studies (which may not be applicable), theoretical drug effects, and author bias. Prospective, double-blinded comparative studies are critical to determine the true efficacy of antithrombotic agents in feline CE.

Primary Prevention

CLOPIDOGREL (PLAVIX) OR ASPIRIN. Clopidogrel has more potent antiplatelet effects than aspirin in multiple species including cats and demonstrates significantly better efficacy against arterial thrombosis in human beings, although this is distinctly different from CE. Adverse effects generally are similar to aspirin in human patients and none have been reported in cats. Although considerably more expensive than standard aspirin therapy, clopidogrel is comparable with the low-dose aspirin protocol that requires compounding. Clopidogrel is available orally and administered only once daily. Clopidogrel has never been studied in primary CE prevention in cats.

Aspirin is extremely cheap when given at the standard-dose protocol, available orally, administered only once every 2 to 3 days, and safe in cats although gastrointestinal adverse effects can be seen. The use of a lower dose can help to reduce these adverse effects. The use of a very low–dose protocol (5 mg/cat PO q72h) requires compounding and increases the cost considerably. Splitting the tablet into fourths can be used as an alternate low-dose protocol while maintaining cost effectiveness. Aspirin has never been studied in primary CE prevention in cats.

CLOPIDOGREL-ASPIRIN COMBINATION THERAPY. The combination of clopidogrel and aspirin could be used to induce a greater antiplatelet effect. This has gained interest in human medicine recently for prevention of CE associated with atrial fibrillation and is the focus of a clinical trial in which combined therapy is being compared to warfarin.[129] This may allow comparable efficacy while reducing adverse effects and lack of diligent monitoring. Both are available orally and at a relatively low cost. The combination would likely have low adverse effects except a possible increased risk for bleeding. Clopidogrel-aspirin combination therapy has never been studied in primary CE prevention in cats.

Secondary Prevention

WARFARIN. Because of the wide interindividual and intraindividual variable dose response, need for diligent therapeutic monitoring, risk for bleeding, and continued elevated recurrence rates, warfarin appears to be a secondary choice for cats at this time. However, with drug compounding and more gradual dose adjustments, bleeding complications may be reduced, whereas more consistent therapeutic anticoagulation may result in reduced recurrence rates. The true efficacy of warfarin has never been studied in secondary CE prevention in cats.

CLOPIDOGREL. Discussion for primary prevention also applies for secondary prevention. Clopidogrel is more cost effective than the LMWH and is available orally. Clopidogrel has never been studied in secondary CE prevention in cats.

LOW-MOLECULAR-WEIGHT HEPARINS. These drugs have been shown to be safe in cats and appear to have similar recurrence rates to other antithrombotic agents.[56,130] They must be given by subcutaneous injections and are the most expensive therapeutic option. They may be cost prohibitive to most owners if they must be administered more than once daily. The true efficacy of the LMWH has never been studied in secondary CE prevention in cats.

CLOPIDOGREL-ASPIRIN COMBINATION THERAPY. This combination also could be used for secondary prevention. The discussion regarding the use of this combination for primary prevention also holds true for secondary prevention. Clopidogrel-aspirin combination therapy has never been studied in secondary CE prevention in cats.

CLOPIDOGREL AND LOW-MOLECULAR-WEIGHT HEPARIN COMBINATION. This protocol would have combined antiplatelet and anticoagulant properties. The risk for LMWH-induced platelet activation also may be reduced, although whether this occurs in cats is unknown. This combination has been used in human beings for acute treatment of arterial thrombosis. The cost of this combination therapy would be higher than either agent by itself but may allow once-daily administration of the LMWH. The combination may result in increased bleeding complications, although this has not been seen in a small number of cats (less than 10).[131] Clopidogrel-LMWH combination therapy has never been studied in secondary CE prevention in cats.

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Chapter 38

Chronic Upper Respiratory Disease: Principles of Diagnosis and Management

John R. August and Anne Bahr

Chronic upper respiratory disease, characterized by recurring sneezing and/or snuffling that is poorly responsive to antimicrobial treatment, is one of the most frustrating clinical problems for cat owners and small animal practitioners. Several factors contribute to our meager success in the management of this disease:

- Our poor understanding of the many causes of chronic upper respiratory disease
- The tendency to consider chronic sneezing and snuffling in all patients as a single clinical entity for which antimicrobial treatment is the preferred therapy
- Our failure to recognize the changing bacterial flora of the diseased upper respiratory tract over time as the process progresses
- Financial and logistical challenges that often prevent diagnostic testing necessary to identify the location and extent of the disease
- Our failure to recognize that many patients require adjunctive surgical therapy to address sequestered infections not amenable to antimicrobial therapy alone
- Difficulties encountered by owners in the long-term administration of oral medications to affected cats

First-time assessment of an affected cat or reevaluation of a current patient that has failed to respond to symptomatic treatment can benefit from a logical approach of answering a series of questions that pertain to that individual patient's illness.

- Which organisms, antigens, irritants, or pathological processes initiated upper respiratory signs in this chronically affected patient?
- Which organisms, antigens, irritants, or pathological processes are present in this chronically affected patient at the time of examination?
- Where is the infection, inflammation, or pathology located at the time of examination?
- Are atypical or uncommon signs present at the time of examination?
- Should the patient be treated medically, surgically, or with both modalities?

INITIATING CAUSES

Often sneezing and/or snuffling has been occurring for months or years by the time the patient is presented for a second opinion. Although it can be difficult for owners to remember the earliest signs associated with their cat's illness, especially after numerous veterinary visits and assorted treatments, important clues may be identified that assist in the formulation of a definitive diagnosis. For example, acute infections with feline herpesvirus-1 (FHV-1) usually are characterized by rhinitis and conjunctivitis, with fever, anorexia, and malaise in young animals[1] (Figure 38-1). Corneal ulceration may occur less frequently. In general, FHV-1 produces a more severe clinical disease than feline calicivirus (FCV).

Acute infections with FCV are characterized by fever, conjunctivitis, and rhinitis that usually are less severe than that seen in FHV-1 infection, in addition to ulcerative glossitis, faucitis, and palatitis. Lameness resulting from immune-mediated polyarthritis may be observed in some acutely infected cats[2] (see Chapter 1).

Chlamydophila felis, known formerly as *Chlamydia psittaci*, primarily is a conjunctival pathogen.[3] Acute infections are characterized by a profuse serous ocular discharge, severe conjunctival chemosis, hyperemia of the palpebral conjunctiva, and blepharospasm.[4] Nasal discharges and sneezing are

Figure 38-1. Acute FHV-1 infection with secondary bacterial rhinoconjunctivitis in a 6-week-old kitten. Note the mucopurulent oculonasal discharges and open-mouth breathing.

uncommon. Ocular discharges may become mucopurulent or suppurative as a result of secondary bacterial infections.[4]

Acute infections with *Bordetella bronchiseptica* occur more commonly in cats from rescue facilities, in patients from households with a larger number of cats, and in cats in contact with dogs with respiratory tract disease. Overcrowding and stress may be important predisposing factors.[5] Clinical signs include sneezing, oculonasal discharges, and coughing.[6] Severe dyspnea, cyanosis, and occasionally death may occur in young kittens as a result of bronchopneumonia.[5] Although coughing is reported less frequently in cats than in dogs with acute *B. bronchiseptica* infections,[5] a history of coughing as an early clinical sign should raise suspicion that this organism may have been an initiating factor in a chronic disease process.

Mycoplasma spp. can be isolated more frequently from the upper airways cats of cats with chronic rhinitis than from normal cats.[7] Presently, the role of *Mycoplasma* spp. in the initiation and/or perpetuation of chronic upper respiratory disease is unclear. Most likely, these organisms colonize respiratory tissues already damaged by other pathogens or noninfectious disease processes.

Cryptococcus neoformans may cause mycotic rhinitis, possibly resulting from asymptomatic nasal cavity colonization.[8,9] Sneezing, epistaxis, and nasal discharges may be noted initially, followed by the appearance of granulomatous lesions at the external nares. Facial deformity may occur secondary to local bone destruction if invasive strains of *C. neoformans* are involved. Clinical signs associated with colonization and infection of the caudal nasal cavity may result from penetration of the cribriform plate and subsequent cryptococcal meningoencephalitis and optic neuritis.[8]

Upper respiratory signs associated with immune-mediated (allergic) rhinitis may be seasonal initially. However, signs may become perennial, with or without seasonal peaks, in patients with expanding spectra of hypersensitivities or in cats with secondary microbial infections.

Patients with nasal or nasopharyngeal foreign bodies (e.g., grass blades that have migrated rostrally from the nasopharynx) often present with a peracute onset of upper respiratory tract irritation, characterized by harsh staccato sneezing or reverse sneezing. Pawing at the face, nose, and mouth also may be noted.

Initial clinical signs in cats with nasal or nasopharyngeal neoplasia may include sneezing, stertor (inspiratory snoring), or epistaxis.

Other clues may be obtained by review of the signalment and environmental background of the patient. A general, reasonable suspicion is that infectious diseases initiated chronic infection if oculonasal signs first arose when the cats were young, or if the cats came from an environment in which infections were prevalent (e.g., a shelter or multiple-cat household with many cats). Conversely, infectious disease would be much less likely when sneezing or snuffling first arises in an adult cat, ocular signs are absent, and in-contact patients show no clinical signs.

CONTRIBUTING CAUSES AT TIME OF EXAMINATION

Although helpful diagnostic information may be acquired from a careful history of the patient's early clinical signs, contributing infectious or noninfectious factors change considerably over time, as a result of the natural progression of the disease and treatments administered. If possible, the patient should be categorized into one of the following groups, based on complete diagnostic evaluation:

- Previous viral infection with persistent secondary bacterial infections
- Persistent viral infection with secondary bacterial infections (e.g., patients with chronic rhinosinusitis and keratitis resulting from FHV-1 or patients with chronic gingivostomatitis resulting from FCV)
- Fungal disease (e.g., infection with *C. neoformans*)
- Persistent microbial infections secondary to infection with feline leukemia virus (FeLV) or feline immunodeficiency virus (FIV)
- Immune-mediated disease with or without secondary bacterial infections
- Anatomical or obstructive diseases (e.g., nasopharyngeal polyps or foreign bodies) with or without secondary bacterial infections
- Neoplastic disease with or without secondary bacterial infections

Secondary bacterial infections usually contribute to all stages of chronic upper respiratory disease induced initially by FHV-1 or FCV. However, the microbial flora of the diseased upper respiratory tract changes associated with chronicity and repeated antimicrobial treatments. Secondary bacterial infections that develop in kittens with acute FHV-1 or FCV disease usually consist of commensal organisms already present in the nasal cavity (e.g., *Staphylococcus* spp., *Streptococcus* spp., and *Pasteurella multocida*). Rational choice of antibiotics for the acutely infected cat therefore is directed by recognition of the composition of this flora.

Based on bacterial cultures obtained by insertion of a brush into the choanae of chronically infected cats using retroflex fiberoptic endoscopy, my* experience is that the microbial flora of the region changes predictably over time. As the disease starts to become more chronic, mixed infections of acute-phase bacteria and *Pseudomonas aeruginosa* become common. With

*One of the chapter co-authors, John R. August.

time and additional nonspecific antimicrobial treatments, *P. aeruginosa* becomes the dominant organism, and monocultures of this organism commonly cause perpetuation of bacterial rhinosinusitis in affected cats. In this respect, the author's experience differs from the observations of other investigators who found that *P. aeruginosa* was cultured from only 13 per cent of cats with chronic upper respiratory disease.[10] In that study, *Pasteurella* spp. (31 per cent) and *Staphylococcus* spp. (23 per cent) were the organisms isolated most frequently.[10] Bacterial cultures obtained from within the choanae by retroflex fiberoptic endoscopy appear to provide a more accurate reflection of the opportunistic microbial flora in chronic bacterial rhinitis than swab cultures taken from the rostral nasal cavity.

Recognition of the importance of *P. aeruginosa* in the perpetuation of chronic upper respiratory infections of cats is one of the keys to understanding why affected cats fail to respond to most antimicrobial treatments, and how more effective therapeutic strategies can be developed.

The prevalence of *P. aeruginosa* in the nasal exudates of chronically affected cats leads to the reflection on the public health significance of this finding. Close contact perhaps should be prevented between *P. aeruginosa*–infected cats that are sneezing and human beings who are particularly susceptible to infection with this organism (e.g., patients with cystic fibrosis).

LOCATION OF LESIONS

Feline practitioners have to be competent ear, nose, and throat specialists if they are to address chronic upper respiratory tract disease effectively. Many cats presenting with refractory signs of sneezing or stertor have lesions extending beyond the nasal cavity (e.g., the frontal sinuses, nasopharynx, or middle-ear cavities).

Recognizing that chronically affected cats may have sequestered infections, often as a result of *P. aeruginosa*, in the frontal sinuses or middle-ear cavities has important implications for therapeutic management and prognosis. Long-term remissions or cure are unlikely in these patients unless aggressive antimicrobial therapy is combined with surgical exploration, curettage, and drainage of the infected cavities.

Unfortunately, physical examination and history provide few clues about the presence of the extent of the disease. Accurate mapping of the affected areas requires oronasal and otic examinations under anesthesia, ocular examination, nasopharyngeal endoscopy, and advanced imaging techniques.

Purely unilateral nasal discharge is more common with fungal, neoplastic, or dental disease, or foreign bodies than with bacterial rhinitis. However, some patients with chronic bacterial rhinitis or rhinosinusitis secondary to viral infection may have asymmetrical nasal discharges.

It is extremely difficult to predict which affected cats have frontal sinusitis in addition to rhinitis and whether one or both sinuses are affected. Cats with bacterial frontal sinusitis present with histories and clinical signs similar to those cats with just rhinitis. However, the attending clinician should have a heightened suspicion of concurrent frontal sinusitis in affected cats that relapse after aggressive antimicrobial treatment directed at *P. aeruginosa.* Anecdotally, frontal sinusitis also should be suspected in refractory patients with paroxysmal sneezing, which results in copious, tenacious, asymmetrical purulent exudates. Some owners report retrospectively that their affected cats are less reclusive and more active after frontal sinus surgery, which suggests that some of these patients quietly suffer significant discomfort. This concept is supported by the observation that frontal sinus exudates sometimes are released under pressure during trephination.

ATYPICAL OR UNCOMMON SIGNS

The foundation for accurate identification of the cause of upper respiratory signs is based on a careful history and physical examination. Skipping these fundamental procedures in favor of laboratory or imaging studies, or because of time constraints, frequently causes important clues to go unnoticed.

Respiratory Noises

The process should start with a clarification of the reason for the visit. Clients sometimes present their cat erroneously for "sneezing," a sound attributed traditionally to inflammation or disease of the rostral nasal cavity. Careful questioning may determine that these patients may be reverse sneezing or exhibiting stertor, signs often associated with disease of the nasopharynx. With practice and a temporary loss of dignity and decorum in the examination room, mimicking these various respiratory noises is possible, which ensures that client and clinician are in agreement about the sounds made by the affected cat.

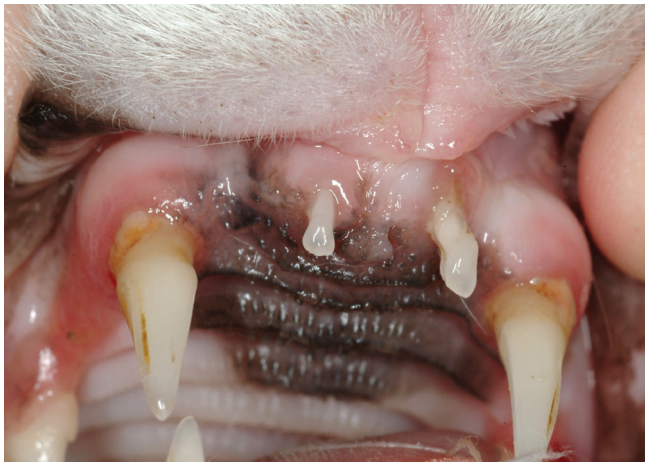
Compared with cats with disease localized primarily to the nasal cavity in which nasal discharge and forward sneezing are common signs, cats with nasopharyngeal disease more commonly are presented with signs of stertorous respiration, weight loss, and voice change.[11] In a series of 53 cats with nasopharyngeal disease, 49 per cent had lymphosarcoma (mean age = 10.7 years), and 28 per cent were affected with nasopharyngeal polyps (mean age = 3.0 years). Palpable soft palate masses were found in 82 per cent of the cats,[11] which reinforces the importance of a thorough oral examination in all cats with chronic upper respiratory disease.

Some patients may be presented with a combination of respiratory sounds; for example, forward sneezing and reverse sneezing, or reverse sneezing and stertor. Diffuse nasal diseases in cats and dogs can spread to the nasopharynx, which causes irritation in both areas.[12] Cats with lymphoplasmacytic or allergic rhinitis may exhibit these respiratory patterns.

Open-mouth breathing may occur in cats with bilateral rhinitis associated with severe turbinate swelling and copious nasal discharges, in patients with proliferative nasal cavity disorders such as neoplastic or fungal diseases, and in cats with nasopharyngeal stenosis. In the latter case, scar tissue occludes the choanae progressively as a result of chronic upper respiratory tract infections.[13] A balloon dilation technique has been described to relieve respiratory obstruction in cats with nasopharyngeal stenosis.[14]

Oral Lesions

A thorough oral examination is an essential part of evaluation of the cat with chronic upper respiratory disease. The dental arcade should be observed carefully to determine if advanced periodontal disease and tooth root abscesses may be the cause of nasal discharges (Figure 38-2). Similarly, the oral cavity should be evaluated carefully in stertorous cats for asymmetrical changes suggestive of fungal or neoplastic disease. The



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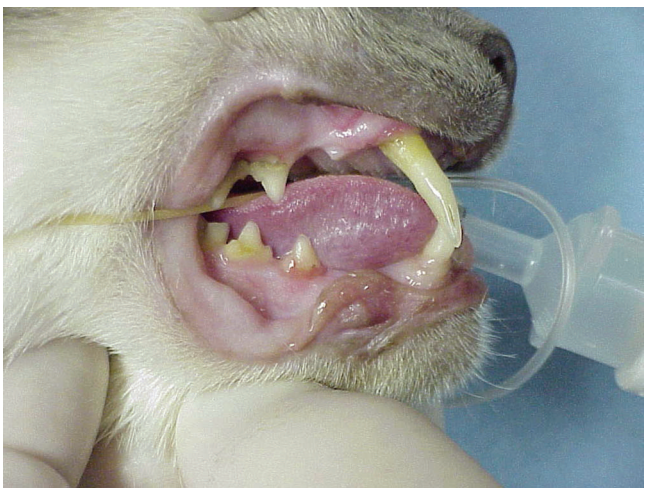

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Figure 38-2. A, Severe periodontal disease and tooth loss in a 1-year-old FeLV-positive cat presented for reluctance to eat and sneezing. **B,** Periodontal disease, supererupting maxillary canine teeth, and an odontoclastic resorptive lesion on tooth 407 in a 10-year-old spayed female Siamese cat.

junction of the soft and hard palates is a common location for bulging enlargements associated with nasopharyngeal neoplasms[7] (Figure 38-3). Failure to identify significant oral lesions on cursory physical examination often leads to missed diagnoses in cats with chronic upper respiratory disease.

Chronic lymphoplasmacytic gingivitis may be associated with the chronic carrier state of FCV.[15,16] Early lesions (Figure 38-4, *A*) may be indistinguishable from other causes of lymphoplasmacytic gingivitis such as bacterial plaque intolerance. Advanced lesions may be more ulceroproliferative, which affect the gingiva of the caudal dental arcade and fauces preferentially (Figure 38-4, *B*) (see Chapter 1). Pain may preclude a thorough examination of the oral cavity without sedation or anesthesia.

Nasal and/or Facial Distortion

Conformational changes of the nose and face rarely, if ever, result from bacterial rhinitis unless an apical tooth root abscess is present. Anatomical distortions usually are associated with

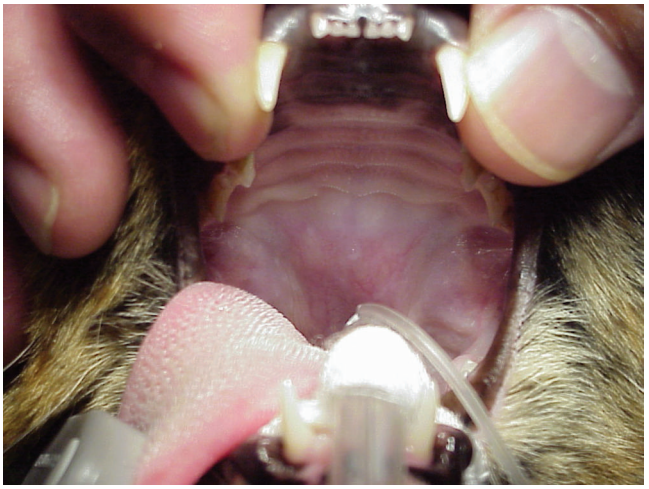
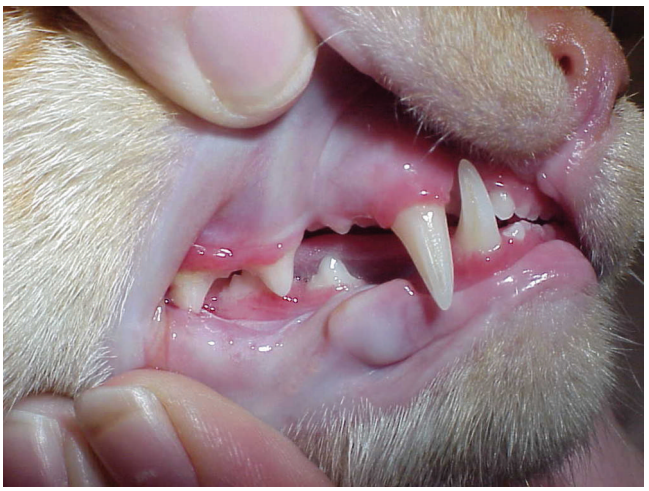


Figure 38-3. Protruding bulge at the junction of the hard palate and soft palate in a 5-year-old spayed female domestic shorthair cat presented for epistaxis and nasopharyngeal stertor. Histopathological diagnosis was basosquamous cell carcinoma.



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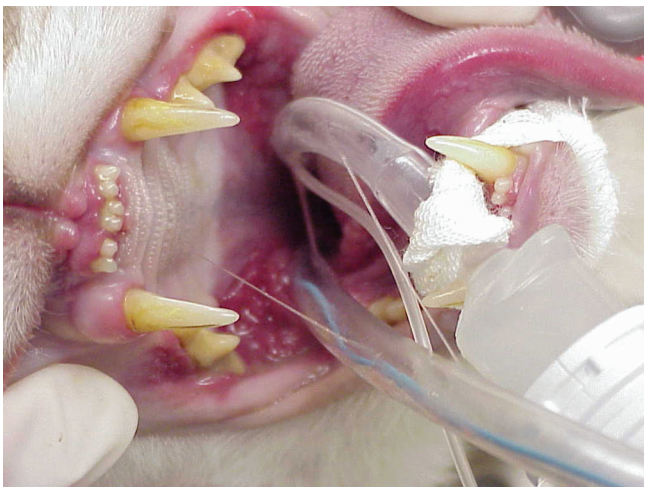


B

Figure 38-4. A, Diffuse gingival swelling and hyperemia in a 6-month-old neutered male domestic shorthair cat. Gingival disease developed progressively after a relatively mild upper respiratory tract infection. FCV was cultured repeatedly over time from the gingival margin and fauces. **B,** Severe faucitis, gingivostomatitis, and periodontal disease in a chronic carrier of FCV.

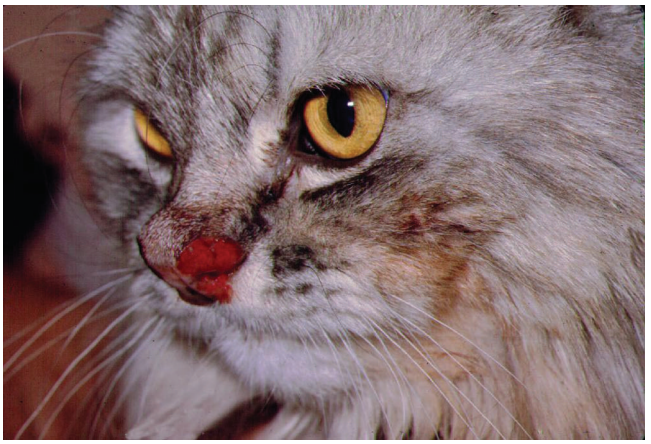


Figure 38-5. Bilaterally symmetrical, ulcerating granulomatous lesions around the nares of a 7-year-old neutered male Persian cat with *Cryptococcus neoformans* infection of the rostral nasal cavities. Organisms were identified in impression smears of exudates from the ulcerated surfaces.

fungal (Figure 38-5) or neoplastic change and are associated with a guarded prognosis. Asymmetrical changes, such as ocular proptosis, may be subtle and missed easily unless the patient's face is examined closely from a position in front of the cat.

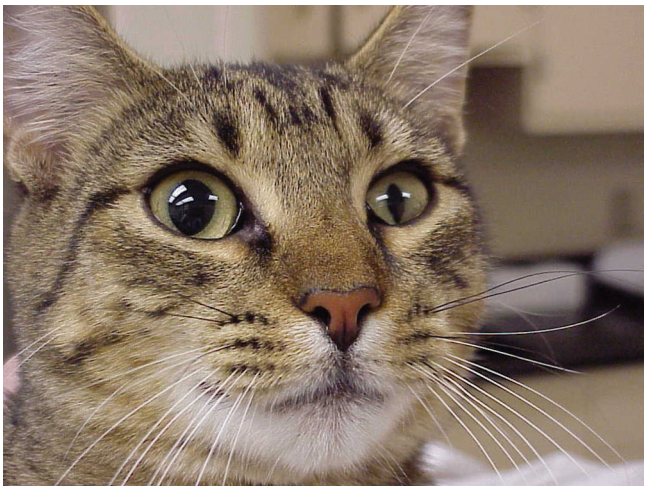
Ocular Signs

A complete ophthalmic examination is an important part of the comprehensive evaluation of cats with chronic upper respiratory disease. Chronic herpetic keratitis may be a sequela of the FHV-1 carrier state. Lesions, which may be unilateral, consist most commonly of nonulcerative keratitis with stromal infiltration of inflammatory cells and blood vessels, which lead to fibrosis and scarring with deep and superficial vascularization. Ulcerative keratitis is less common.[1] Other lesions that may be associated with chronic FHV-1 infection include corneal sequestra, eosinophilic keratitis, and idiopathic uveitis[1] (see Chapter 3). Some cats with chronic FCV infection have subtle bilateral conjunctival erythema and mild epiphora, in addition to previously described gingival changes.

A fundic examination should be performed on all cats presented with chronic upper respiratory disease, especially those patients with atypical signs such as nasal or facial deformities or stertorous respiration; for example, optic neuritis may occur as a result of invasive cryptococcal infection.[8]

Neurological Signs

Cats with stertorous breathing may have concurrent neurological signs, which facilitate the localization of the lesion in the respiratory tract (see Figure 56-12). Nasopharyngeal polyps most likely originate in the middle ear cavity and are composed of inflammatory granulation tissue covered with respiratory epithelium.[17] The factors initiating polyp development are not well understood. Polyps may arise as a congenital defect of the first pharyngeal pouch. Conversely, the lesions may be the result of a chronic inflammatory response in the middle ear cavity induced by upper respiratory virus infection.[17] With use of polymerase chain reaction testing, no evidence of tissue persistence of FHV-1 and FCV was found in polyps from 21 cats,



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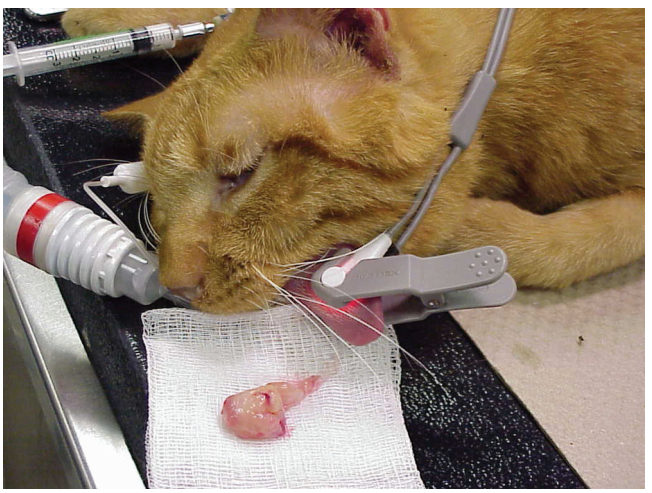


B

Figure 38-6. A, Horner's syndrome in a 7-month-old male domestic shorthair cat presented because of stertorous respiration. A large nasopharyngeal polyp was removed by traction. **B,** An external ear canal polyp, removed by traction, that had extended into the horizontal canal from the middle ear cavity through the tympanic membrane. The 10-month-old neutered male cat was presented because of otorrhea and otic pain. Bacterial otitis media was present.

which suggests chronic viral infection was not responsible for the development of the lesions.[18]

Polyps arising in the middle ear cavity may extend by a stalk down the eustachian tube into the nasopharynx, remain in the middle ear cavity, or migrate through the tympanum into the horizontal ear canal. Clinical signs in affected cats include stertorous respiration, sneezing, nasal discharge, dysphagia, epistaxis, weight loss, Horner's syndrome (miosis, ptosis, enophthalmos, and protrusion of the nictitating membrane) (Figure 38-6), head tilt, otic discharges, and pawing at the ear(s)[17,19] (Figure 38-7). If the nasopharyngeal polyp is large enough to cause intermittent laryngeal obstruction, respiratory stridor and syncope may occur. Rhinitis with sneezing may be the result of changes in upper respiratory airflow as a result of obstruction caused by a polyp.[19]

Optimal management of middle ear polyps depends on the location of the lesion, owner finances, the determination by imaging of whether otitis media is present, and the availability of surgeons skilled in ventral bulla osteotomy. Recurrence is

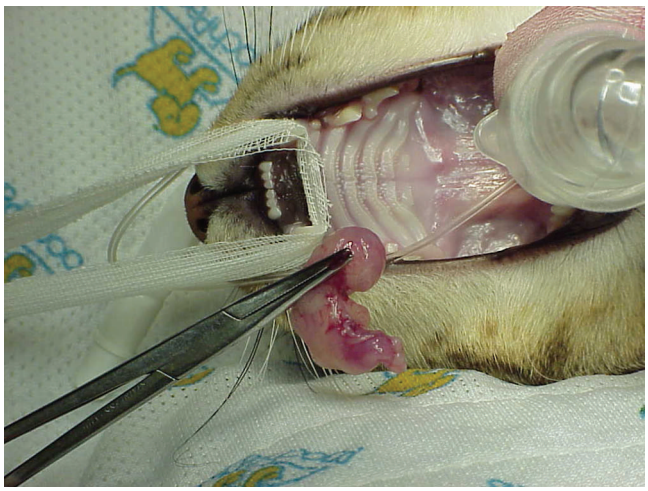


Figure 38-7. Polyp from patient in Figure 38-6, *A*. The polyp caused episodic laryngeal obstruction, which led to brief periods of syncope.

less likely when traction of the polyp is followed by ventral bulla osteotomy,[20] especially when middle ear cavity and external ear canal disease are present.[21] Careful consideration must be given to possible anesthetic and postoperative complications in patients with large polyps undergoing ventral bulla osteotomy.[19] Recurrence of nasopharyngeal polyps after traction alone was reduced when the affected cats were treated concurrently with corticosteroids.[21]

Deafness

Owners of cats with chronic upper respiratory disease, especially patients with histories suggestive of nasopharyngeal disease, should be questioned about their cat's ability to hear. Primary otitis media may develop as a result of ascending bacterial infections resulting from upper respiratory tract infections (Figure 38-8). Secondary otitis media may occur when middle ear polyps rupture through the tympanic membrane and extend into the external ear canal.[22] Ascending infections from the nasopharynx may result from eustachian tube dysfunction secondary to the presence of nasopharyngeal polyps (Figure 38-9).

Cats with bilateral effusive otitis media tend to sleep more and to ignore trigger factors that normally attract their attention (e.g., the can opener being used in the kitchen, dry food being poured into their dish, and their owners returning home). Occasionally, owners of cats with otitis media report their cats assume unusual positions-of-relief in response to the discomfort and they make gagging sounds, associated presumably with drainage of middle ear exudates into the nasopharynx.

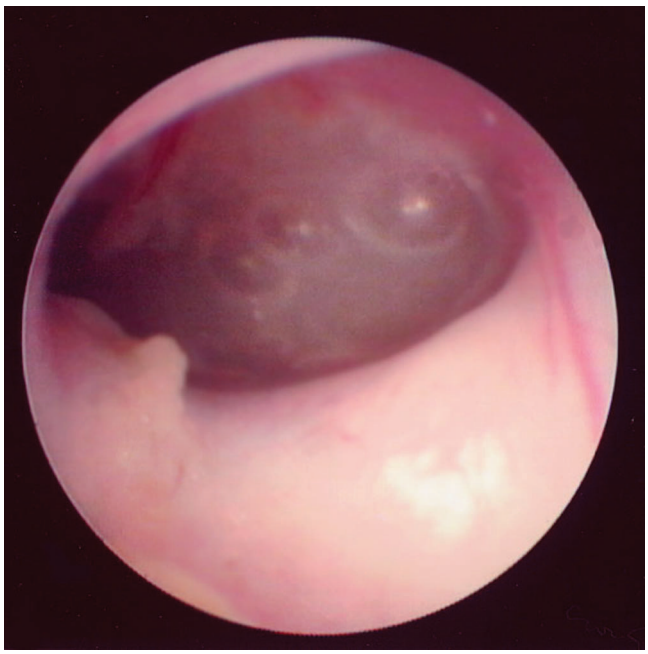


Figure 38-8. Video-otoscopic view of the tympanum of a 1-year-old neutered male Siamese cat presented with chronic signs of snuffling, gagging, and deafness after an earlier upper respiratory virus infection. Bilateral effusive otitis media was found otoscopically and with CT scans (see Figure 38-16, *B*). Note the bulging tympanum, vascularization around the perimeter of the tympanum, and bubbles within fluid in the middle ear cavity. Bilateral ventral bulla osteotomies were performed. Cultures of middle ear effusion were negative for bacterial growth; the patient recently had finished a 4-week course of treatment with oral azithromycin.

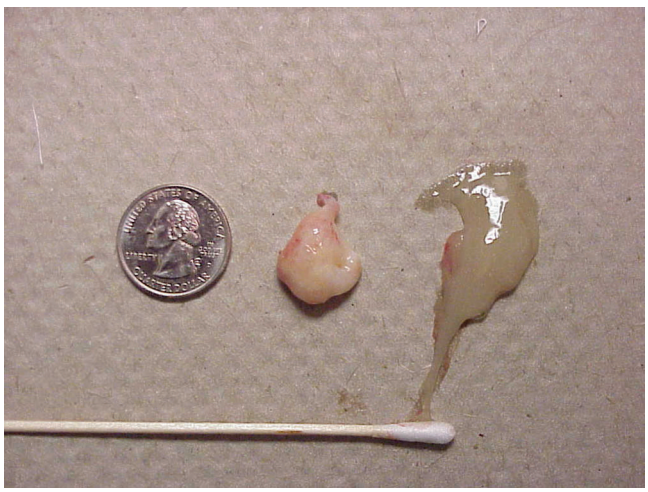


Figure 38-9. Flocculent mucoid exudate from the middle ear cavity retrieved from the nasopharynx of a cat after removal of an inflammatory polyp by traction. (Courtesy Alice M. Wolf, Texas A&M University.)

PATIENT EVALUATION

The extent of the diagnostic evaluation recommended for patients with chronic upper respiratory disease depends on clues identified on history and careful physical examination and on owner finances. Gold-standard recommendations include the following[7]:

- Complete blood count, serum biochemistries, and urinalysis
- FeLV and FIV tests
- *C. neoformans* serum antigen titer
- Thoracic radiographs to identify lower respiratory tract lesions secondary to upper respiratory tract disease, or vice versa
- Detailed oral, fundic, and deep otic examinations, and evaluation of patency of each nostril[7]
- Cytological evaluation of nasal exudates from patients with signs suggestive of infection with *C. neoformans*

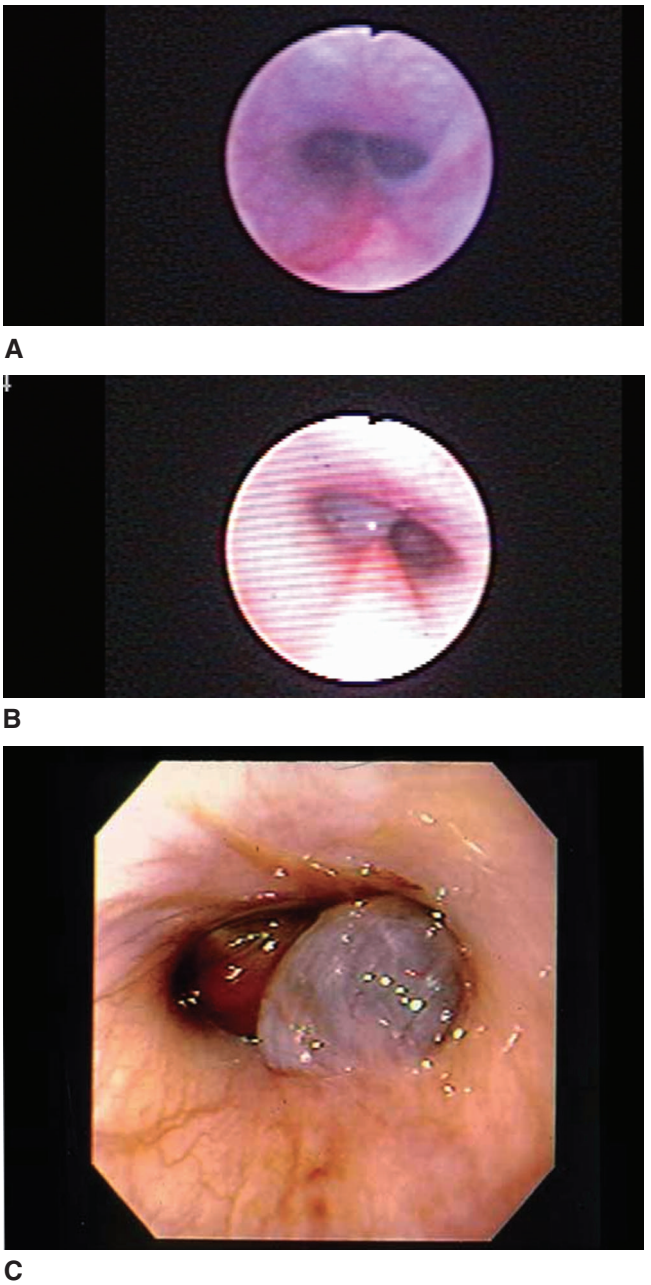


Figure 38-10. A, Normal feline choanae. Note the endoscopic brush inserted into the choanal orifice. **B,** Unilateral mucoid discharge in the choana of a cat with chronic rhinitis. **C,** Asymmetrical, proliferative, neoplastic mass obstructing the choanae. (Photographs courtesy Debra L. Zoran, Texas A&M University.)

- FCV culture from gingival tissues, especially if faucitis is prominent
- PCR tests from conjunctiva for FHV-1, if strongly suspicious ocular lesions are present[1]
- Lateral nasopharyngeal radiographs, if nasopharyngeal polyps or masses are suspected
- CT imaging of nasal cavity, frontal sinuses, and osseous bullae (see section below)
- Retroflex fiberoptic endoscopy of the nasopharynx and choanae[23] (Figure 38-10)
- Brush cytology of choanal exudates and mucosal surfaces[24]
- Brush samples of choanal exudates for aerobic and anaerobic bacterial culture and *Mycoplasma* culture
- Pinch biopsies of mass lesions in choanae for bacterial and fungal culture, and for histopathology with special stains

Rostral Rhinoscopy

Special consideration for examination of the rostral nasal cavities should be given to patients with unilateral nasal discharge, animals with a suspected history of nasal foreign body or obstructive disease suggestive of tumor, or cats with clinical findings suspicious of fungal disease.[25] Fungal plaques may be observed on the turbinate mucosa of cats with nasal and frontal sinus infections caused by *Aspergillus* spp. and *Penicillium* spp.[26]

Turbinate Mucosal Pinch Biopsies

In one study, cytological findings from the nasal mucosa correlated with histopathological findings in only 25 per cent (three of 12) of cats with nasal disease.[27] Cytologic changes suggested an acute inflammatory response in 11 of 14 cats with chronic disease in the same study, which reflects collection of cells from the superficial mucosa. In another study, poor correlation was noted between rhinoscopic findings and the severity of inflammation in biopsy specimens of nasal turbinate mucosa.[28] Additionally, the type of inflammation identified on histopathological examination was not correlated with rhinoscopic signs of inflammation. The results of both studies reinforce the importance of turbinate mucosal biopsy to complement rhinoscopy in the thorough evaluation of cats with nasal disease. Turbinate mucosal biopsy is necessary to identify cats with primary lymphoplasmacytic rhinitis with chronic secondary bacterial infection. As noted previously, bacterial cultures taken from the choanae appear to reflect the pathogenic microflora of the diseased nasal cavity more accurately than cultures taken from the mucosal surface of the rostral nasal cavity.

Imaging Studies

Imaging modalities that are used commonly to evaluate cats with upper respiratory disease include radiography and the cross-sectional imaging modalities: computed tomography (CT) and magnetic resonance imaging (MRI). In the past, radiography has been the mainstay of evaluation because of its ubiquitous availability. However, CT and MRI are becoming more available to the general practitioner and therefore the pros and cons and the usefulness of these modalities are discussed.

Radiography

Proper positioning of nasal and skull radiographs is imperative for ease of interpretation. Therefore these types of views should be obtained with the patient under general anesthesia to allow for precise positioning. Typical views obtained to evaluate the skull and nasal cavities completely include the ventrodorsal or dorsoventral (VD or DV), lateral (RtLeL or LeRtL), 20-degree obliques from lateral (Le20-V-RtDO or Rt20 V-LeDO), rostrocaudal (RCd) and rostrocaudal open mouth (R30 V-CdDO), and

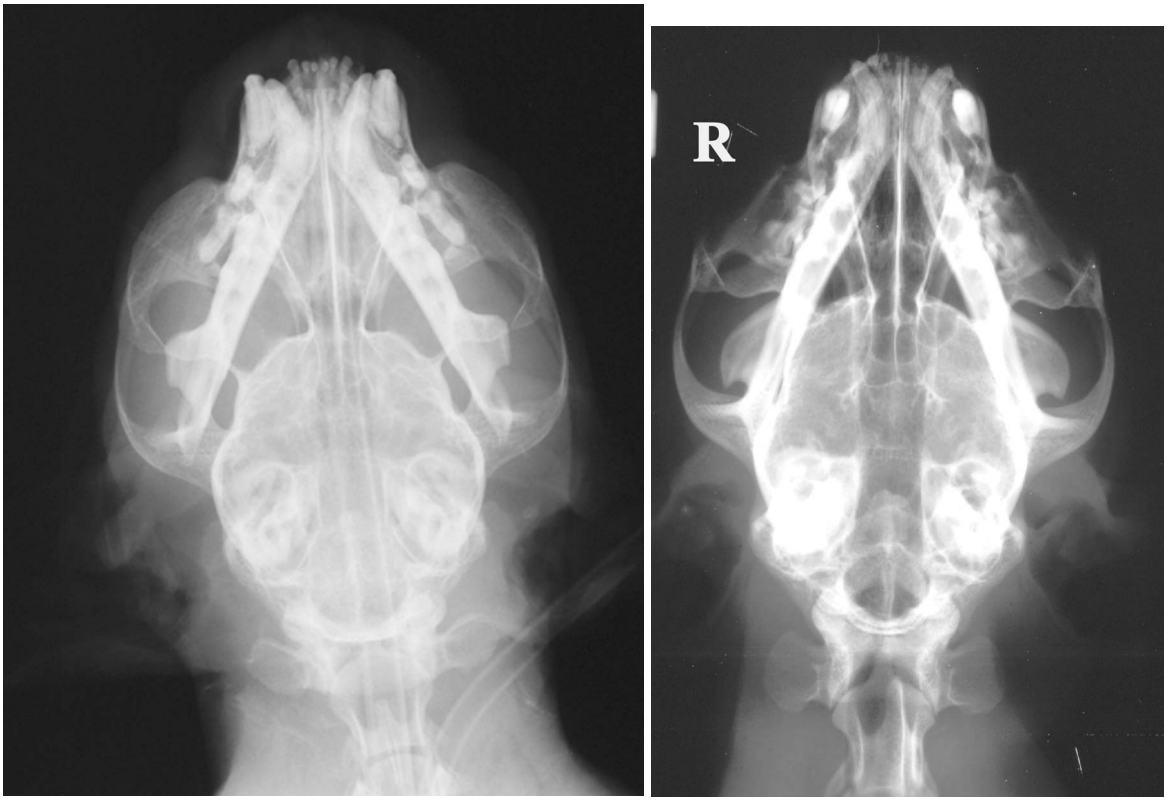


Figure 38-11. A, Normal DV radiograph of the skull of a cat. Note the symmetry of the hemimandibles and tympanic bullae consistent with appropriate positioning. **B,** DV radiograph of a cat showing increased opacity of the right tympanic bulla consistent with otitis media. Note that because of superimposition of the mandible, evaluation of the nasal cavities is difficult on this view.

intraoral views. The intraoral or VD/DV view often is helpful if the disease is affecting the nasal cavity. The rostrocaudal view is best for evaluation of the frontal sinuses but may be difficult to obtain in breeds with short noses. The lateral view is best for evaluation of the pharynx when looking for polyps. The reader is referred elsewhere for a detailed description on how to obtain these images.[29]

Abnormal sinonasal radiographic findings basically can be grouped into the following pattern categories:

1. Normal radiographic appearance of both nasal passages
2. Areas of increased soft tissue opacity superimposed over a normal conchal pattern
3. Areas of increased soft tissue opacity superimposed over areas of conchal destruction
4. Areas of decreased opacity resulting from conchal destruction without accompanying soft tissue opacity
5. Mixed pattern of 2 to 4 above[30]

The distribution and severity of these findings then can be used to provide a ranked differential diagnosis list of possible etiologies.

To create a ranked differential diagnosis list, nasal diseases can be grouped into two basic categories: nondestructive rhinitis and destructive rhinitis. In general, nondestructive rhinitis is caused by benign, nonaggressive etiologies (e.g., disease associated with allergic inflammation or bacterial infection). The radiographic abnormalities associated with nondestructive rhinitis typically include normal radiographs or pattern 2. In this situation, changes in opacity often are seen in the more rostral portions of the nasal cavities (Figure 38-11).

Destructive rhinitis usually is associated with malignant or aggressive diseases (e.g., neoplasia, fungal infections, or occasionally longstanding bacterial rhinitis). This category often is associated with patterns 3 to 5. In addition, neoplasia often is seen in the caudal nasal passage in the area of the ethmoid turbinates and cribriform plate. One recent study found that destructive rhinitis caused by neoplasia commonly caused displacement of midline structures and had unilateral generalized soft tissue opacity and loss of turbinate detail, in addition to invasion of the paranasal bones.[31] Because of overlap of radiographic findings between nondestructive and destructive rhinitis, a biopsy always is necessary for definitive diagnosis. In many cases, imaging is more useful to help guide sample acquisition location in addition to correlate histopathological findings.

Cross-Sectional Imaging

In recent years, the availability of cross-sectional imaging (CT and MRI) has become more widespread. In dogs, CT is superior to radiography in defining the extent of nasal disease in addition to aiding in the ranking of the differential diagnosis

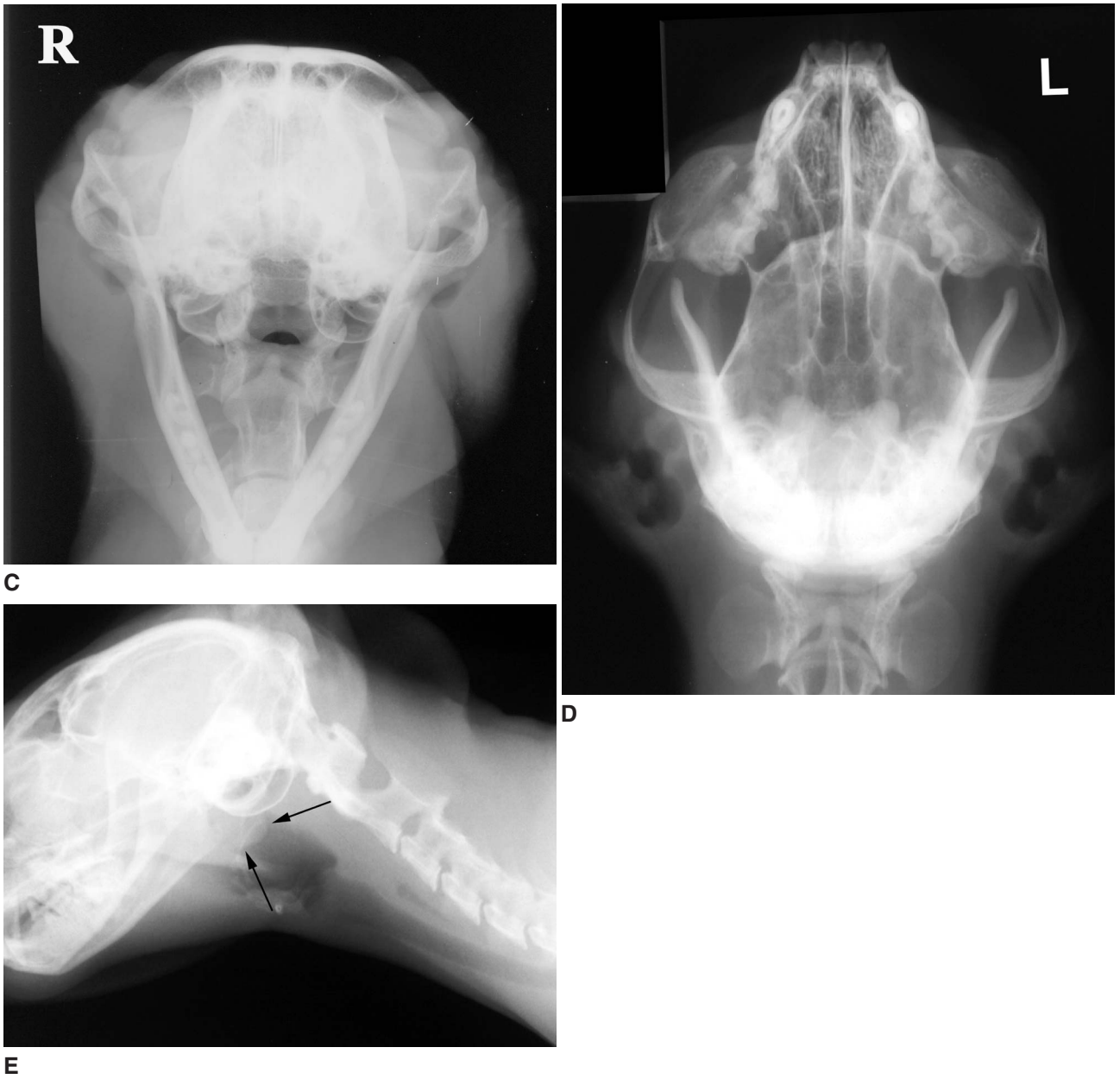
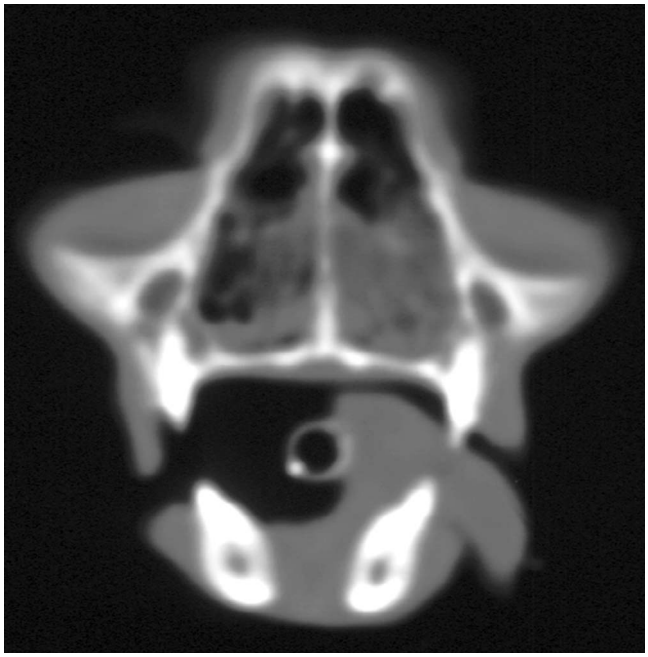


Figure 38-11.—cont'd. C, Open-mouth view (R30 V-CdO) of the same cat in Figure 38-13, *B,* showing mild increased opacity and thickening of the right tympanic bulla. Note that comparison of opacity between the bullae is easier on this view than on the DV view. **D,** Open-mouth view (V20-R-DCdO) of a cat with mild increased opacity of the left nasal passage without any evidence of turbinate destruction consistent with nondestructive rhinitis. **E,** Lateral radiograph of a cat with a large soft tissue mass in the nasopharynx *(black arrows),* which resulted from a nasopharyngeal polyp.

list.[32,33] In cats, CT is not more sensitive than radiography at detecting the presence of nasal disease; however, CT was more sensitive at determining the extent and location of the disease process.[34] The changes seen on CT are similar to those discussed when evaluating radiographs; however, because of the lack of superimposition of structures, determination of the affected areas is easier. For this reason, CT has become the preferred imaging modality in evaluation of sinonasal disease. MRI also can be used to evaluate sinonasal disease, but it is not as sensitive to bone changes because it depicts bone as a signal void and therefore usually is considered less suitable than CT. However, MRI does provide better soft tissue evaluation in addition to elimination of superimposition and thus can be employed if necessary.[35]

As in radiography, an overlap of CT findings occurs between nondestructive and destructive rhinitis (Figure 38-12). However, osteolysis of the paranasal bones is more likely to be seen with neoplastic conditions (Figures 38-13 and 38-14). Very thin bones (such as seen in the orbits of cats) may appear lytic on CT images because of volume-averaging artifact, and this is a consideration in evaluation for bone lysis in this region. Remodeling and sclerosis of the paranasal bones (particularly



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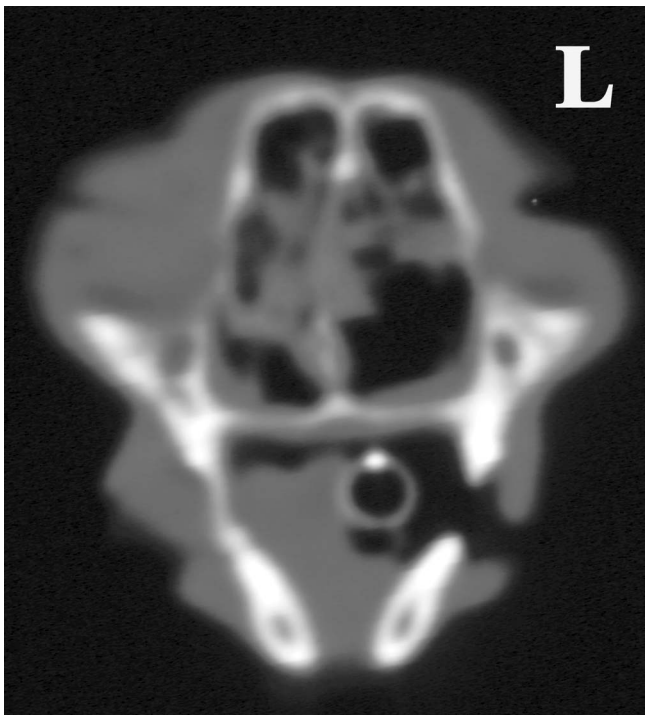
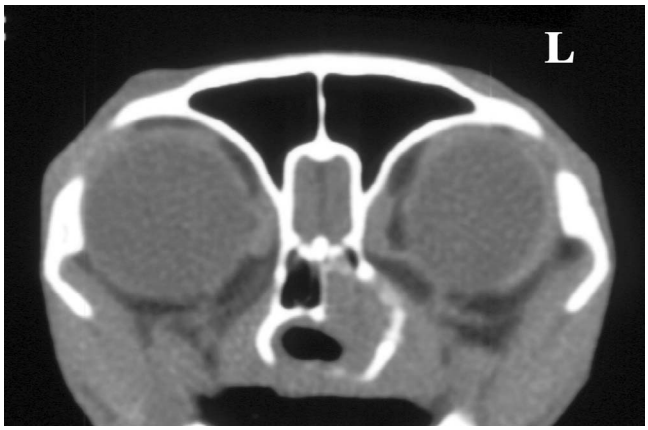


B

Figure 38-12. A, 3-mm axial CT image of a cat with bacterial rhinitis. Note the increased soft tissue attenuating material within both nasal cavities. **B,** 3-mm axial CT image of another cat with bacterial rhinitis. This case shows significant turbinate destruction of the left ventral choana.



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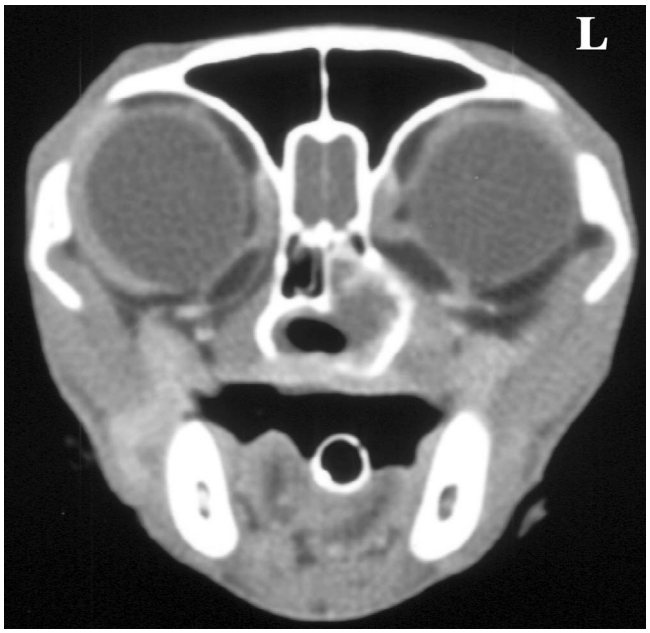

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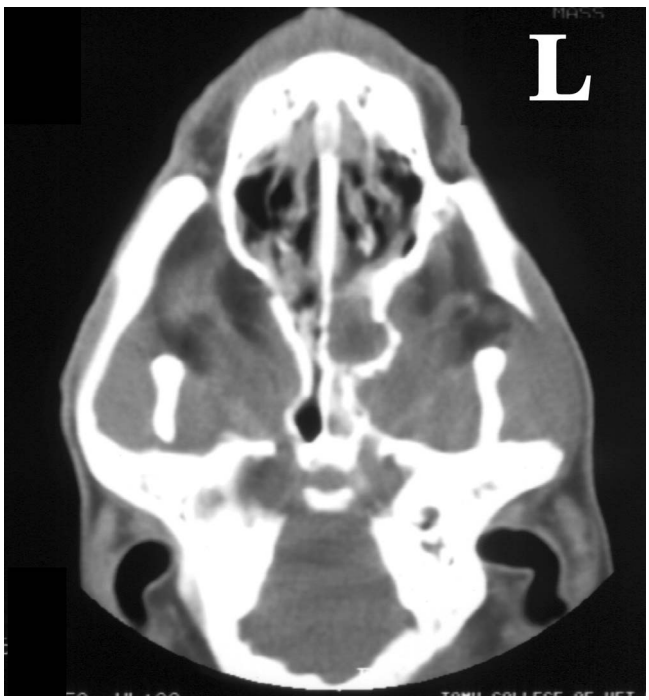
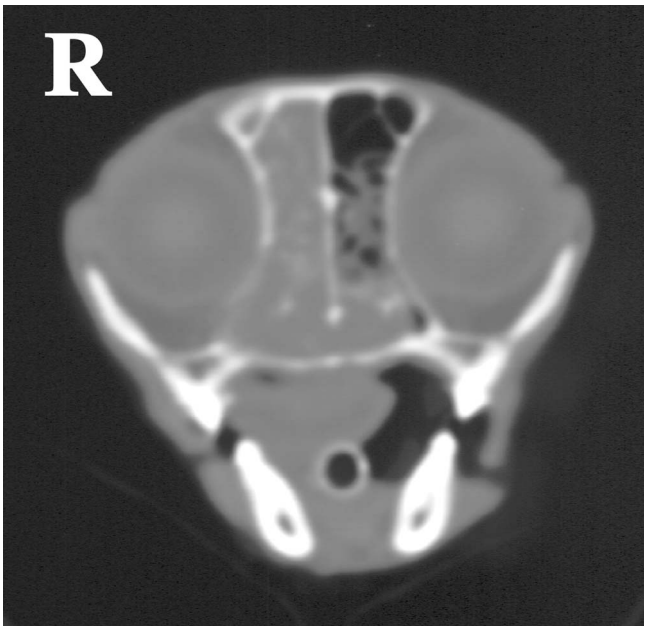


C

Figure 38-13. A, 3-mm axial CT image of a 5-year-old spayed female domestic shorthair cat that presented with inspiratory stertor. Note the lysis of the left palatine and presphenoid bones. This lysis would be suggestive of neoplasia. The histopathological diagnosis was basosquamous carcinoma. **B,** Contrast-enhanced 3-mm axial CT slice of the same cat in Figure 38-13, *A*. Note the peripheral contrast enhancement. **C,** 3-mm dorsal CT image of the same cat in Figure 38-13, *A*. This plane provides a unique perspective on the location and invasiveness of the tumor into the orbit.



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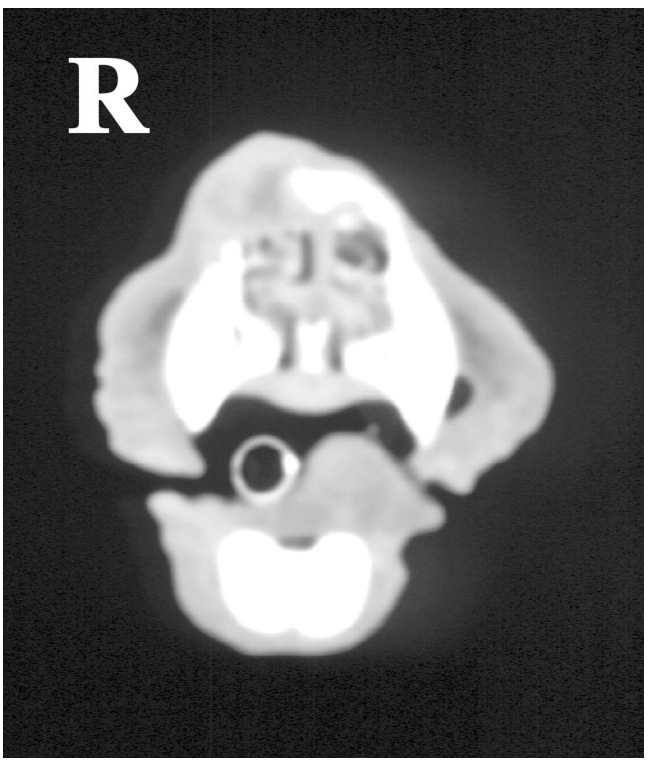


B

Figure 38-14. A, 3-mm axial CT image of a 7-year-old spayed female domestic shorthair cat. Note the extensive lysis of the medial aspect of the right orbit and also of the palatine bone. Histopathological diagnosis was transitional respiratory epithelial carcinoma. **B,** 3-mm axial contrast-enhanced CT image of an 11-year-old neutered male domestic shorthair cat. Note the extensive lysis of the right nasal bone with extension of a soft tissue mass from the right nasal cavity to the superficial surface of the nose. Histopathological diagnosis was chondroblastic osteosarcoma.

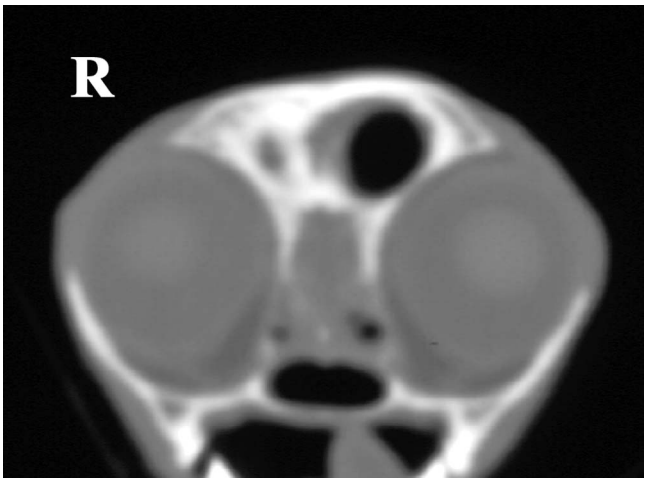


Figure 38-15. 3-mm axial CT image of a cat with remodeling and thickening of the frontal bones with increased soft tissue attenuating material in the sinus, consistent with longstanding nondestructive rhinitis/sinusitis.

the frontal bones) are seen more commonly with nondestructive rhinitis, such as that seen with chronic bacterial diseases (Figure 38-15).[34]

Evaluation of the frontal sinuses and tympanic bullae is performed easily via cross-sectional imaging. These structures normally are air-filled, and replacement of the air with soft tissue attenuating material is a particularly important finding when planning appropriate therapies (see below) (Figure 38-16). The appropriate slice thickness (usually less than 5 mm) and window setting (more than 1000 CT numbers) are critical so that the tympanic bullae do not appear thickened artifactually.[36] Evaluation of the frontal sinuses and tympanic bullae is indicated especially in cases of infectious rhinitis that are refractory to therapy, because infections in these locations may not respond well to medical management.

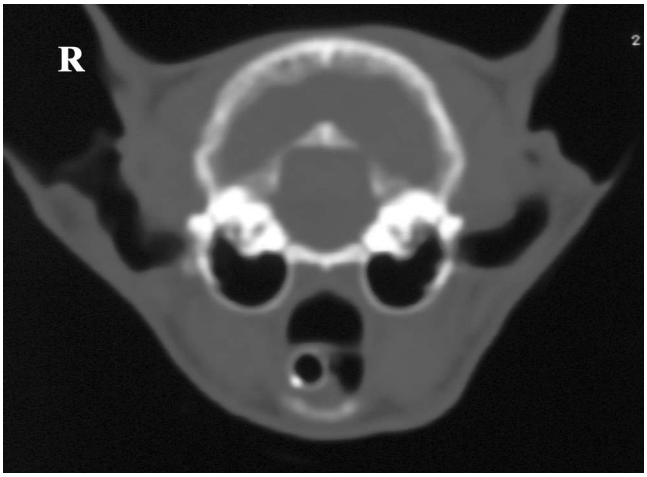
Finally, masses in the nasopharynx can be identified on cross-sectional imaging studies; however, they often are identified easily on lateral radiographs or through direct inspection. Therefore a more expensive modality usually is not necessary for identification of the polyp but may be helpful in evaluation of the tympanic bullae, which also may be affected.

MEDICAL AND SURGICAL TREATMENTS

By the time many affected cats are presented for second opinion, numerous antimicrobial treatments usually have been tried with varying success, and further symptomatic treatments are unlikely to be effective. Recommendations about optimal treatment strategies are based on the outcome of all aspects of a complete diagnostic evaluation, with particular emphasis on the results of diagnostic imaging.

Surgical Management

Patients with rhinitis or nasopharyngitis usually are treated medically, unless primary mass lesions associated with neoplasia or *C. neoformans* are present. Surgical debulking of nasopharyngeal cryptococcomas facilitates response to



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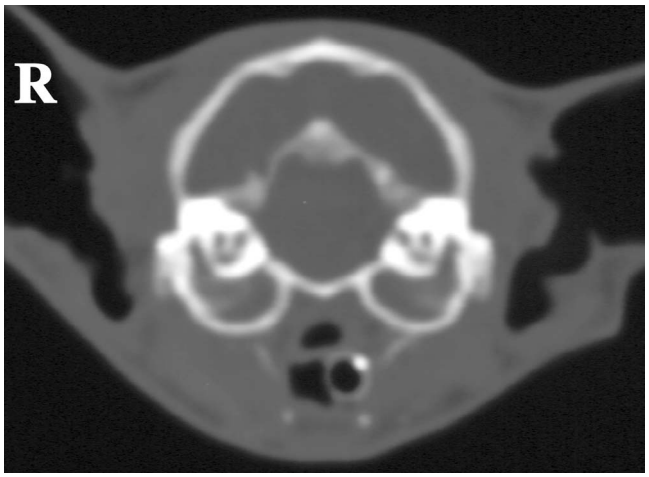

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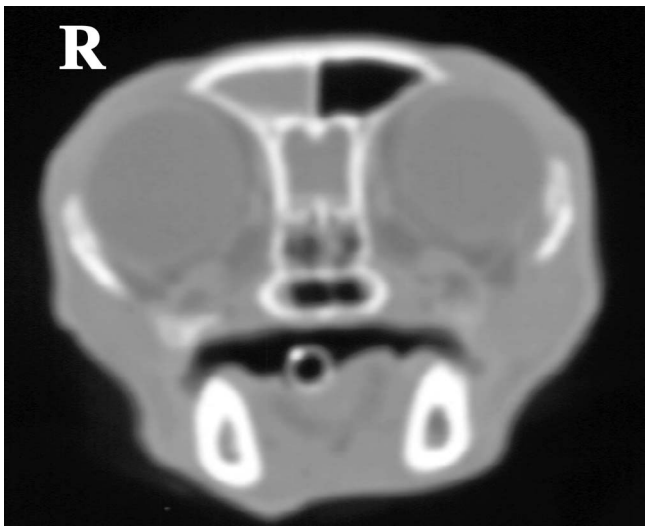

C

Figure 38-16. A, 3-mm axial CT image of a cat with normal tympanic bullae. Note that the bullae are symmetrical and air filled. **B,** 3-mm axial CT image of a cat with soft tissue attenuating material within both tympanic bullae. Diagnosis: otitis media (same patient as in Figure 38-8). **C,** 3-mm axial CT image of a cat with unilateral right frontal sinusitis. Note the normal air-filled appearance of the left frontal sinus.

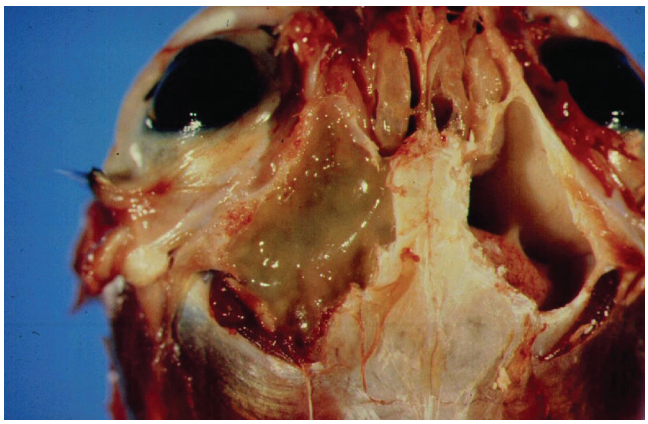

Figure 38-17. Necropsy specimen of a 1-year-old FeLV-positive domestic shorthair cat presented for chronic refractory nasal discharges and sneezing following presumptive FHV-1 infection. Note the bilateral swelling and distortion of the nasal turbinate bones and mucous membranes. The mucosal lining of the left frontal sinus is inflamed, and the sinus cavity is filled with a tenacious, purulent exudate. A pure culture of *P. aeruginosa* was obtained from the frontal sinus exudate.

systemic antifungal therapy.[8] The indications for surgery, chemotherapy, and radiation therapy in the management of intranasal neoplasia in cats are reviewed elsewhere.[37]

Some cats with refractory upper respiratory disease have bacterial infections that are sequestered in the frontal sinuses or middle ear cavities. Relapses or recurrences of clinical signs result from failure of antimicrobials to penetrate infected cavities that contain tenacious, inspissated exudates that drain poorly, especially when infected with resistant organisms such as *P. aeruginosa* (Figure 38-17). Although frontal sinus trephination, curettage, and lavage have not retained widespread support in the treatment of chronic upper respiratory disease, the procedures are an important part of the overall management of cats with rhinosinusitis documented by CT scans (Figure 38-18). Prolonged remissions of clinical signs may be obtained after frontal sinus trephination and specific long-term antimicrobial treatment that otherwise would not be obtained with medical treatment alone. Complications from the procedure are minimal, especially if nasal exudates are flushed caudally into the nasopharynx preoperatively, which prevents postoperative subcutaneous emphysema at the site(s) of trephination. Reduction of further entrapment of exudates within the sinus cavities is reduced by enlargement of the normal drainage opening between frontal sinus and nasal cavity. The sinus cavities are not ablated with fat or other substances during surgery.

Ventral bulla osteotomy is recommended for cats with nasopharyngeal polyps to minimize chances of recurrence, for all patients with polyps extending through the tympanum into the external ear canal, and for cats with clinical signs of nasopharyngeal disease and evidence of middle ear involvement on CT scanning or otoscopy. The reader is referred to the recent literature for descriptions of the surgical technique and possible complications of the procedure.[19,20]

Medical Therapy

Comprehensive strategies for the effective medical treatment of chronic upper respiratory disease are based on the following principles.

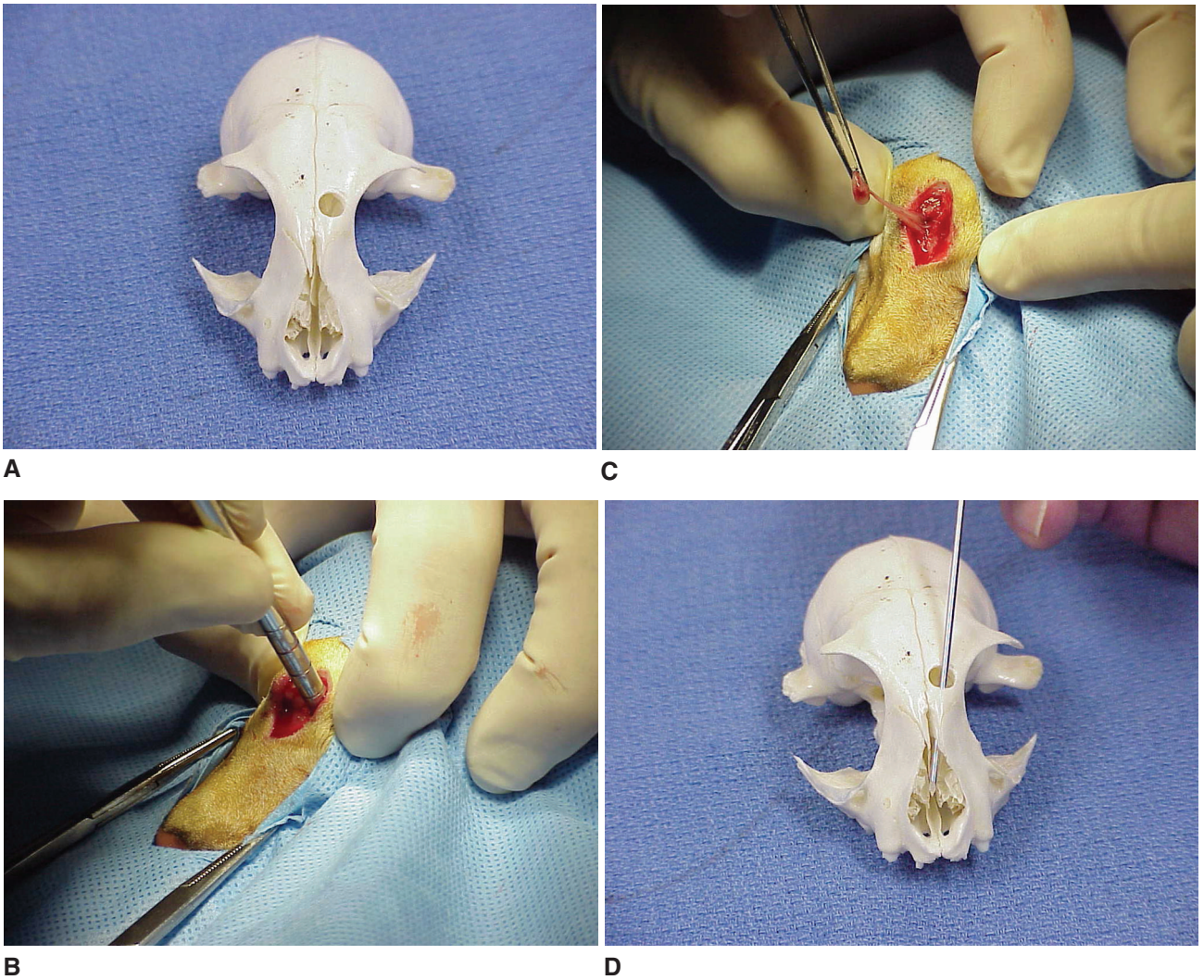

Figure 38-18. **A,** Skull specimen showing location for trephination of the left frontal sinus. **B,** Bilateral frontal sinus trephination through a midline incision. **C,** Tenacious purulent exudates being removed from the left frontal sinus during curettage and lavage. **D,** Skull specimen showing use of Steinmann pin to enlarge ostium between frontal sinus and posterior nasal cavity to promote drainage of secretions and exudates. (Photographs courtesy Bianca Hettlich and H. Philip Hobson, Texas A&M University.)

Treatment should be based on the results of bacterial cultures, antimicrobial sensitivities, and cytologic findings from the posterior nasal cavity (and frontal sinuses or osseous bullae), histopathological findings from nasal mucosal biopsies, and other laboratory tests.

When client resources preclude further diagnostic testing, antibiotic choices should be based on an understanding of the shifting microbial flora of the diseased respiratory tract with time (e.g., a tendency for upper airway colonization with *P. aeruginosa* in chronically infected cats). Conversely, earlier infections may require antimicrobials directed at *Staphylococcus* spp., *Streptococcus* spp., and *Pasteurella multocida*, or at *B. bronchiseptica* if coughing has been a prominent part of the disease.

Antimicrobial treatment should be continued for a minimum of 4 weeks. The decision to extend treatment with specific antibiotics beyond 4 weeks is based on observation of improvement at that time. Ideally, 6 to 8 weeks of treatment should be administered or at least 2 weeks beyond the complete cessation of clinical signs. If no improvement has been noted at 4 weeks, the treatment protocol (and diagnosis) should be reassessed.

Further relapses may be reduced in some cats by the long-term administration each evening of a single q24h dose of the antibiotic that was effective during the initial course of full-dose treatment. Although this dose usually provides only one third to one half of the total daily antimicrobial requirement, it may be enough to control opportunistic secondary infections in some affected cats.

Corticosteroids should be used selectively after careful consideration of the primary diagnosis. Corticosteroids are contraindicated in the treatment of bacterial rhinosinusitis, because they perpetuate bacterial infections, facilitate the shift to more resistant microflora, and may reactivate latent FHV-1 infections. Conversely, oral corticosteroids are an essential part of the management of cats with lymphoplasmacytic rhinitis, many of which have concurrent secondary bacterial infections. Ideally, the secondary bacterial complications should be addressed effectively before long-term corticosteroid treatment

is initiated. Oral methylprednisolone is a suitable choice of corticosteroid for these patients.

Immunostimulant treatments apparently do not induce remission in cats with chronic upper respiratory disease. Similarly, vaccination against upper respiratory pathogens (FHV-1, FCV, and *B. bronchiseptica*) does not alter the course of the disease once established.

Physical therapy plays an important adjunctive role in the comprehensive management of affected cats. Intranasal instillation of therapeutic physiological saline drops helps to liquefy inspissated exudates allowing expulsion.[7] Some cats benefit from exposure to the warm, moist atmosphere of the bathroom when the owner is showering. Although nebulization with antimicrobial agents may reduce signs of infection in some cats with rhinitis, it is unlikely to be successful in patients with frontal sinusitis due to poor penetration.

SUMMARY

Successful management of chronic upper respiratory tract disease in cats depends on a recognition of (1) the wide variety of infectious and noninfectious diseases that can cause sneezing and snuffling in cats; (2) the need for a complete history and careful physical examination as the foundation for the diagnostic process; (3) a comprehensive diagnostic approach to accurately identify anatomical locations affected, primary disease processes involved, predisposing factors to infection, and secondary microbial complications; (4) the role of surgery in some patients to complement medical therapy; and (5) the changing microbial flora of affected tissues over time that guide choices of antimicrobial treatment in chronically affected cats.

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Chapter 39

BRONCHIAL DISEASE

Lynelle R. Johnson

ETIOPATHOGENESIS

The clinical syndrome of feline bronchial disease results from exuberant and persistent inflammation within airways. The etiology of airway inflammation in affected cats is unknown; however, in both human and veterinary medicine, it can be simulated by antigenic or allergic stimulation causing activation of CD4+ lymphocytes and initiation of a Th2 immune response.[1-3] Activation of lymphocytes toward Th2 immunity results in induction of specific cytokines that are protective against parasitic infection or are associated with type I hypersensitivity. In comparison, Th1 adaptive immunity is characterized by increased interferon-gamma and macrophage activating factor, and this arm of the immune system protects against bacterial or viral organisms. Th2 immunity is characterized classically by production of IL-4, IL-5, and IL-13, and IL-5 is particularly important in differentiation and maturation of eosinophils. Degranulation of feline eosinophils results in elaboration of major basic protein, myeloperoxidase, and ribonucleases,[4] and these are responsible for damage and destruction of the epithelial lining of airways (see Chapter 26). Sloughing of pneumocytes exposes sensory and irritant nerve endings to increased types and concentrations of allergens or irritants. Cytokines also may cause increased release of neurotransmitters, and thus inflammatory damage can enhance neural responsiveness. In cats with primarily neutrophilic inflammation, similar toxic damage to airways occurs, followed by the resultant repair process. Recent investigations into the pathophysiology of asthma in several species indicate that inflammation can cause oxidative stress and nitration of proteins, which perpetuate airway injury and proliferative responses.

Characteristic histopathological alterations resulting from the inflammatory response include metaplasia and proliferation of airway epithelium, hyperplasia of mucous glands with production of excess mucus, hypertrophy and hyperplasia of airway smooth muscle, and distal emphysematous changes in the pulmonary parenchyma. In human beings, infiltration of airway smooth muscle cells is being recognized as a specific finding in asthma versus eosinophilic bronchitis[5] and may be responsible for the induction of airway hyperresponsiveness and subsequent airway remodeling. Hyperresponsiveness of airway smooth muscle cells results in airway constriction in response to nonspecific stimuli such as airway irritants, allergens, parasites, or viral particles. Reversible airway constriction is a primary component of the acute asthmatic form of inflammatory airway disease, and this is a feature in some cats with bronchial disease. With chronic and uncontrolled lower airway disease, airway remodeling results in smaller diameter of airways, increased airway resistance, and fixed airway obstruction,[2] and thus some cats display irreversible bronchial changes and expiratory airflow obstruction.

Feline bronchial disease shares many clinical and histological characteristics with human asthma and recurrent airway obstruction (RAO) in horses, although human asthma is associated with eosinophilic airway inflammation, whereas neutrophils predominate in the equine condition. Disease may result from allergic stimulation, hyperresponsiveness to parasitic or fungal elements, or airway irritation associated with inhalation of gastric acid, heavy metals, or particulate matter. Clinical signs may be exacerbated in dirty, dusty, or polluted environments, or in association with upper respiratory tract infections in cats.[6] Although genetic influences in the development of asthma have been established in human medicine, this has not been investigated in cats. Despite many similarities in this condition across species, certain differences also are noted. For example, leukotrienes are implicated in the pathogenesis of certain forms of human asthma; however, leukotriene metabolites are not increased in bronchial fluid or urine of cats with experimentally induced allergic airway inflammation.[7]

CLINICAL SIGNS

Clinical signs of feline bronchial disease include chronic cough, lethargy, exercise intolerance, loud breathing, rapid or labored respirations, and acute respiratory distress. These signs may be acute in origin or may be chronic, nonprogressive problems. The cough associated with lower airway inflammation typically is harsh and associated with active abdominal effort. Owners may believe that the cough represents an attempt to remove a hairball, or they may suspect that a foreign object is stuck in the throat. Coughing can be intermittent or present only during exposure to certain environmental stimuli, or it may be relatively constant. Determining the association of cough with specific trigger events can be an important part of the effort to control clinical signs.

Some cats with respiratory disease exhibit exercise intolerance or lethargy. Reduced play activity or panting or open-mouth breathing after light exercise could be clues to

underlying airway disease. Interestingly, some owners of cats with bronchial disease complain of loud respirations or detection of wheezing sounds from their cat. Cats may be observed to breathe more rapidly than expected or to exhibit difficulty breathing. These signs may be chronic or intermittent in nature.

A subset of cats develops acute bronchoconstriction and displays episodes of respiratory distress, persistent tachypnea, cyanosis, or collapse. Some of these cats may have a previous history of cough or labored respirations, whereas others previously were considered healthy.

PHYSICAL EXAMINATION

Cats with airway disease generally are young to middle age at the development of clinical signs and usually are in good health other than their respiratory signs. Some cats may be overweight because of inactivity associated with exercise intolerance or a reluctance to play. Observation of the respiratory pattern before examination can be helpful in the diagnosis. Although some cats may display only tachypnea, others may have prolonged expiration or an expiratory/abdominal push. This respiratory maneuver is an indication of lower airway narrowing or obstruction and increased expiratory effort.[8] Cats with chronic airway disease that have substantial airway and parenchymal remodeling may display a barrel-chested appearance and decreased thoracic compressibility because of overinflation and emphysema.

Cough is a common feature of feline bronchial disease, and detection of a cough in the cat that presents with respiratory distress or tachypnea is a major clue to the presence of underlying inflammatory airway disease. Affected cats show variable degrees of tracheal sensitivity following palpation. Caution is advised during palpation of the trachea to avoid excessive stress for the cat.

Auscultation of the respiratory tract reveals harsh lung sounds, inspiratory crackles, or expiratory wheezes in 65 to 100 per cent of cats[6,9]; however, the absence of such sounds does not rule out inflammatory airway disease because cats can appear normal between episodes. Tracheal auscultation may reveal gurgling sounds resulting from the presence of excess secretions; however, stridor is not anticipated in a cat with lower airway disease.

DIFFERENTIAL DIAGNOSIS

The primary differential diagnoses to consider are those that cause cough and those that result in tachypnea or labored respirations. Cough may be an indication of parasitic pneumonia (secondary to lungworms *Aelurostrongylus abstrusus* or *Eucoleus aerophila*) or could be suggestive of heartworm disease (see Chapter 36). Cats with heartworm infections can have concurrent vomiting in the history and also may have a heart murmur. Cough can be a sign of an airway foreign body, and this may or may not be obvious on thoracic radiographs. Cough and abnormal respiratory rate or effort also are associated with lower respiratory tract infection caused by bacterial or *Mycoplasma* infection.[10] Fungal pneumonia is less likely to result in cough in cats.

Tachypnea and labored respirations can be indicative of inflammatory airway disease but also may be consistent with upper airway obstruction, cardiac disease, pleural effusion, and pulmonary inflammation or pneumonia. Tachypnea resulting from upper airway disease (laryngeal mass or paralysis) is associated with inspiratory effort and stridor. Cardiac disease with pulmonary edema would be supported by concurrent detection of a heart murmur or gallop rhythm; however, some cats with heart disease lack auscultatory abnormalities. An important distinction between cats with lung versus heart disease is the presence of a cough, because cats with congestive heart failure typically do not cough. Pleural effusion resulting from cardiac disease or other causes also can result in tachypnea. The physical examination finding of absent lung sounds ventrally would be typical in those cases, whereas increased lung sounds are expected with bronchial disease. Tachypnea also is found in cats with infectious or atypical pneumonia. In cats with infectious causes of pneumonia, systemic and naso-ocular signs also are common, although fever is detected in less than 20 per cent of cases.[10,11]

DIAGNOSIS

Inflammatory bronchial disease should be considered a diagnosis of exclusion. Bronchial disease is considered highly likely when chronic cough or acute onset of respiratory distress is found in a young to middle-age cat. Because idiopathic inflammatory airway disease generally requires long-term management with corticosteroids and/or bronchodilators, diagnostic efforts are aimed at ruling out infectious etiologies and primary causes of airway inflammation.

The minimum database rarely contributes to the diagnosis of feline airway disease; however, the presence of eosinophilia is suggestive of asthma in a cat with relevant clinical signs. Asthma has been reported as one of the top causes of peripheral eosinophilia in cats, although many affected cats display neutrophilia resulting from chronic inflammation. In cats with peripheral neutrophilia, ruling out lower respiratory tract infection is particularly important because this has been a consistent finding in two recent studies.[10,11]

Although airway parasites and heartworm disease are identified uncommonly in cats presenting to our hospital with respiratory disease, complete diagnostic testing for these conditions is wise to rule out a primary cause of airway inflammation. Fecal flotation is performed to detect the double-operculated egg of *Capillaria aerophila* (also known as *Eucoleus aerophilus*), whereas a Baermann examination is used to detect larval stages of *Aelurostrongylus* spp. At least 1 gram of a fresh, unrefrigerated fecal sample must be submitted for Baermann evaluation.

Tests for heartworm disease should be considered in some cats presenting with cough, particularly when vomiting also is in the history, or when the cat is from an area in which feline heartworm disease has been identified (see Chapter 36). Detection of large pulmonary arteries on thoracic radiographs is a definite indication that heartworm disease should be ruled out; concurrent pulmonary infiltrates may or may not be present. Heartworm disease can be diagnosed by the appearance of parallel lines in the pulmonary artery or right heart with echocardiography.[12] A positive heartworm antigen test is a highly specific test and is indicative of heartworm disease. The ELISA antigen test detects the presence of a protein that originates from the female heartworm's reproductive tract. This test typically becomes positive 5 to 7 months after infection. However, the test can be negative because of a low worm burden or presence of only male heartworms, and therefore this is more of a

diagnostic test than a screening test. The heartworm antibody test for cats detects exposure to the developing larvae of heartworm and therefore is a reasonable screening test for exposure. Antibodies are found approximately 2 to 3 months after infection; however, a cat with heartworm infection may be antibody-negative occasionally. In addition, the antibody test can be falsely positive because it will remain positive for some time after adult heartworms have died. Because of the difficulty in determining infection, use of heartworm antibody and antigen testing could be supported in relevant areas. In a cat with large pulmonary arteries, obtaining an echocardiogram also is wise to detect heartworm infection.

Radiographs play an important role in documenting airway disease and excluding other causes of cough; however, normal thoracic radiographs do not exclude idiopathic airway disease as a cause for clinical signs in affected cats. The classic finding in cats with airway disease is peribronchial infiltrates; lung hyperinflation, flattening of the diaphragm, increased space between the diaphragm and heart, or aerophagia also may be seen. Some cats may display only a mild interstitial pattern, and lobar collapse (primarily of the right middle lung lobe) or focal alveolar infiltrates can be seen in some cats because of mucus plugging of large airways with secondary atelectasis (Figure 39-1). In an evaluation of 25 cats with bronchial disease, a primary bronchial component to the radiographic infiltrate was apparent in 75 per cent of cases; however, alveolar infiltrates were described in 60 per cent.[9] Alveolar infiltrates generally are presumed to indicate pneumonia; however, they are not pathognomonic. A bronchial pattern was reported in 40 per cent of cats with lower respiratory tract infection, and 36 per cent had bronchoalveolar infiltrates in a recent study.[10] Therefore peribronchial radiographic changes should not be considered pathognomonic for idiopathic feline bronchial disease.

Computed tomography (CT) provides additional information on the degree of mucus accumulation in smaller airways and air trapping by allowing three-dimensional reconstruction of thoracic structures (Figure 39-2). CT also has enhanced sensitivity for detection of airway wall thickening, mucus obstruction, emphysematous changes, and secondary bronchiectasis.

In the stable patient, airway fluid analysis is recommended to exclude primary causes of cough and airway inflammation. A transoral tracheal wash or bronchoscopy can be used to collect fluid. Pretreatment with terbutaline (0.01 mg/kg SQ) for 12 to 24 hours before the procedure may improve the safety of the procedure by initiating bronchodilation before anesthesia. For a transoral tracheal wash, the cat is sedated for intubation with a sterile endotracheal tube. A sterile, 5- to 7-French polypropylene or red rubber catheter is passed to the level of the carina (approximately at the fourth intercostal space), and 3 to 5 ml of warmed, sterile saline are injected and then aspirated. Retrieval of 0.5 to 1.0 ml is sufficient for cytological analysis and culture. For bronchoscopy, a small endoscope (preferably 2.5 to 3.8 mm outer diameter) is safest to use and easiest to manipulate within the airways of cats. The cat is anesthetized with intravenous agents (e.g., propofol) and oxygen supplementation is supplied through jet ventilation or with an oxygen cannula passed down the trachea. The endoscope is passed through the trachea and all airways are examined. Cats with bronchial disease typically have viscid secretions within airways. Cats usually do not display mucosal hyperemia as do dogs with bronchitis; however, the epithelial surface may appear irregular, granular, or nodular.

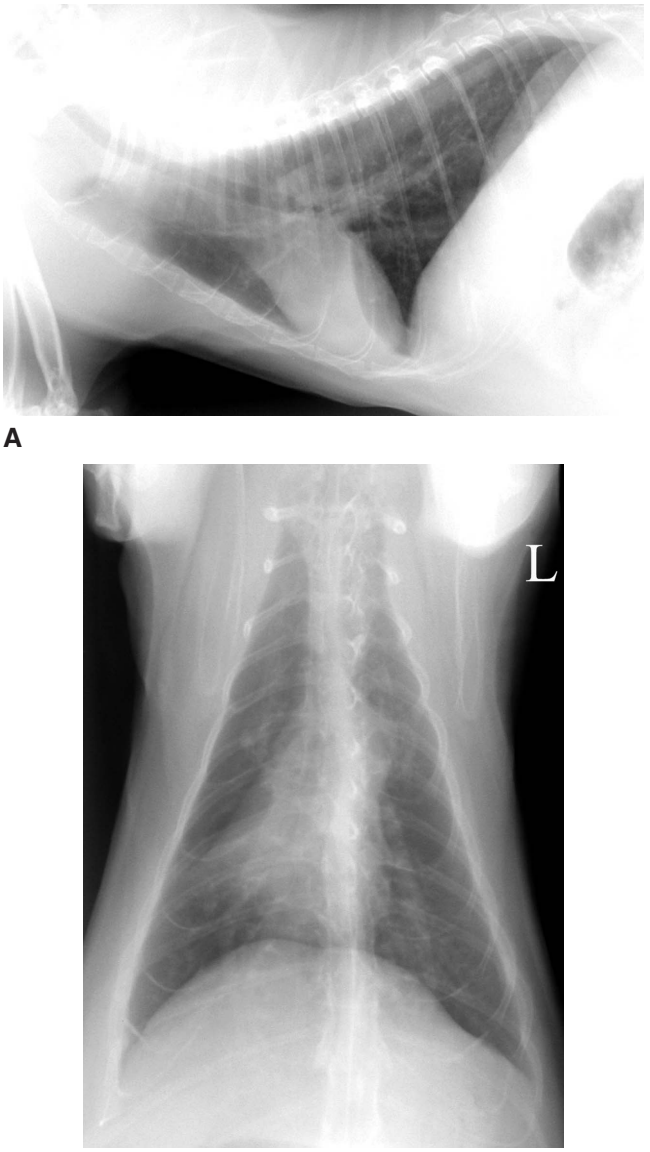
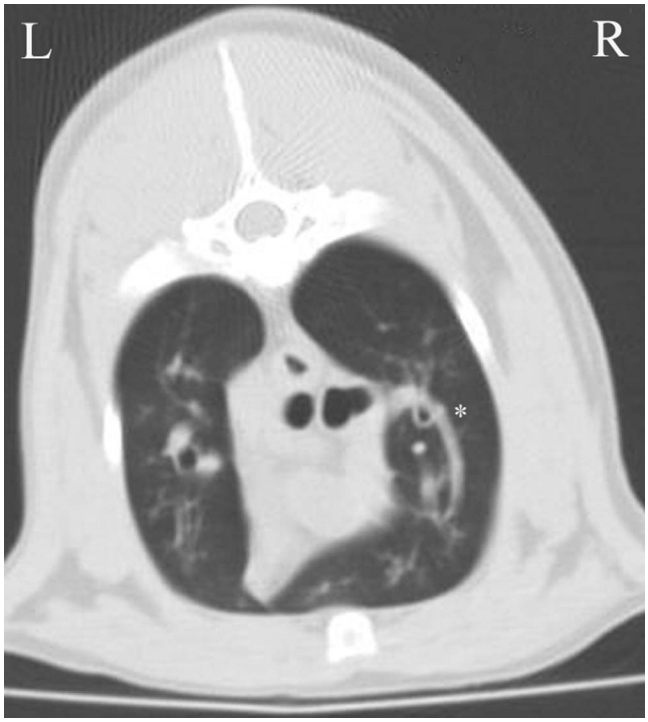


Figure 39-1. A, Left lateral radiograph of a cat with chronic bronchial disease. A lobar fissure line is noted in the region of the right middle lung lobe. **B,** DV radiographic view of the same cat, noting right middle lung lobe consolidation. In both views, a pronounced peribronchial infiltrate is detected by visualization of increased numbers of parallel airway walls and by increased thickness of airways seen in cross-section.

Before obtaining bronchoalveolar lavage (BAL) fluid for culture and cytology, the endoscope is removed from the airway, the biopsy channel is rinsed, and the outer surface is wiped free of contamination. BAL is performed by wedging the endoscope gently in a small airway, instilling a 3-ml to 10-ml aliquot of warmed, sterile saline, and retrieving the fluid by gentle aspiration. If insufficient fluid is obtained, a second aliquot is instilled at the same site. The presence of foam within the fluid indicates that it contains surfactant and therefore has been in contact with the alveolar surface.

Cats with idiopathic lower respiratory tract inflammation can have primarily neutrophilic or eosinophilic cytology (Figure 39-3). The significance of the primary cellular infiltrate



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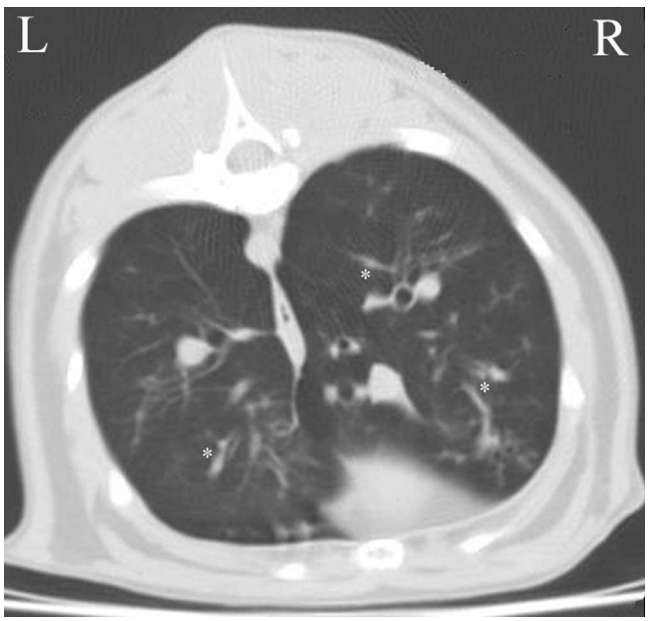

B

Figure 39-2. 5-mm slices from a helical CT performed on the cat shown in Figure 39-1. **A,** CT slice is made through the region of the right middle lung lobe. On the right side of the chest, an opaque curvilinear marking *(asterisk)* represents filling of the right middle lobar bronchus with mucus. **B,** Cross-section located in the caudal thorax. Multiple small airways are filled with mucus *(asterisks),* thickened airway walls can be seen, and hyperinflation is present.

currently is unknown, and in two recent studies more cats had primarily neutrophilic inflammation than eosinophilic inflammation.[6,9] Light growth of bacteria from the lower airways of cats with and without bronchial disease is common, occurring in approximately 75 per cent of healthy or bronchitic cats.[6,9] True infection typically is associated with systemic signs of

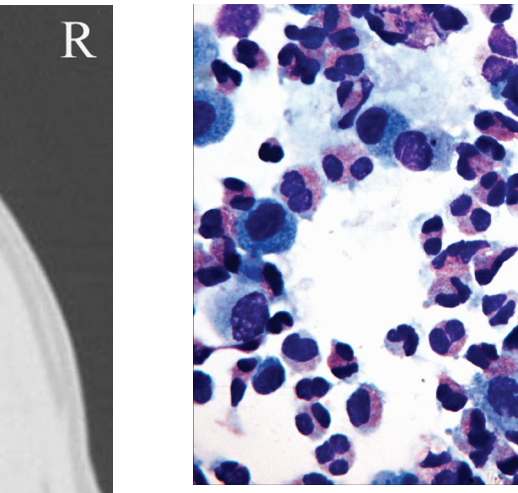

Figure 39-3. Granulocytic bronchoalveolar lavage cytology from a cat with chronic bronchial disease (100×). The differential cell count in this cat was characterized by 82 per cent eosinophils (normal <25 per cent).

illness, degenerative or septic airway cytology, and a positive response to antimicrobial therapy.[10]

The role of *Mycoplasma* infection in respiratory disease remains controversial. It has been isolated from tracheobronchial lavage samples in 21 to 66 per cent of cats with various types of lower respiratory disease[10-13] but not from bronchoalveolar lavage samples of healthy cats.[13] Aerobic and *Mycoplasma* cultures always should be performed in cats with cough or tachypnea, because *Mycoplasma* spp. are a common finding in cats with lower respiratory tract infection,[10] and because of the possibility that *Mycoplasma* spp. may worsen airway hyperreactivity.

Pulmonary function tests to evaluate airway resistance and lung compliance or flow-volume relationships can be performed at certain referral institutions. Many cats with bronchial disease exhibit higher airway resistance than healthy cats because of relative bronchoconstriction. Administration of terbutaline decreases resistance in some affected cats, indicating partial reversibility of smooth muscle contraction.[6] Cats with bronchial disease also exhibit airway hyperresponsiveness to a nonspecific aerosol stimulant, as evidenced by a reduction in the dosage of methacholine required to increase airway resistance.[6] Whole body plethysmography (in a sealed and calibrated plexiglass box) recently has been proposed as a method to document airway hyperreactivity in awake, spontaneously breathing cats by measurement of box pressure signals (expiratory time and peak inspiratory and expiratory flows) and calculation of enhanced pause, a variable that correlates with airway resistance.[14] Plethysmography is technically challenging, and measured variables are influenced by respiratory rate and the animal's age.

Tidal breathing flow volume loops (TBFVL) are used commonly to evaluate pulmonary function in noncompliant human pediatric patients and also have been used to investigate respiratory flow characteristics in cats with bronchial disease. This procedure provides a measure of expiratory and inspiratory flows and volumes during normal respiration in awake, unsedated cats. The cat breathes through a facemask attached to a pneumotachograph and pulmonary mechanics analyzer. Pressure measured at the pneumotachograph is proportional to flow

through the mask, and signals are integrated over time to determine volume at each cycle of respiration. TBFVLs in cats clinically affected by bronchial disease exhibit defects in expiratory flow consistent with bronchoconstriction, which supports the presence of airflow obstruction in these cats. Significant findings in cats with bronchial disease included increased expiratory:inspiratory time ratio, decreased peak expiratory flow rate, and decreased tidal breathing expiratory volume.[8]

TREATMENT

Emergency

Diagnostic tests should be kept to a minimum initially for the cat presenting with signs of acute bronchoconstriction such as cyanosis, tachypnea, and open-mouth or abdominal breathing. Stabilization can be achieved by providing an oxygen-enriched environment and using parenteral administration of a β_2 agonist such as terbutaline. This drug alleviates bronchoconstriction by opposing smooth muscle contraction and is effective in cats with airway disease that have reversible airway constriction.[6] It is an effective bronchodilator with few cardiac side effects, it is a relatively safe drug, and it is easy to administer subcutaneously, intramuscularly, or intravenously at 0.01 mg/kg. An additional dose can be administered after 30 minutes if insufficient response is noted.

Epinephrine, a sympathomimetic agent, is a potent bronchodilator but should be used only when cardiac disease has been excluded from the differential diagnosis list because α and β_1-adrenergic stimulation can result in adverse side effects of cardiac arrhythmias, vasoconstriction, and systemic hypertension. Aminophylline is a weak bronchodilator and its use in an emergency situation may not be justified because other drugs are more likely to be effective. Also, intravenous aminophylline injection can be associated with anaphylaxis, and intramuscular or subcutaneous routes of administration cause pain on injection.

Respiratory rate and effort should be monitored visually in the first hour of observation to determine a therapeutic response. If the cat does not respond to terbutaline, use of a short-acting corticosteroid (dexamethasone-SP or Solu-Delta-Cortef at standard doses) often results in rapid alleviation of clinical signs caused by inflammatory airway disease. Use of corticosteroids affects further diagnostic testing because these drugs decrease migration of inflammatory cells into the airway; however, corticosteroids may be required to stabilize the animal. If the cat fails to respond to these measures, causes for respiratory distress other than idiopathic bronchial disease should be investigated.

Management

Antiinflammatory Agents

Inflammation is believed responsible for the pathogenesis of feline bronchial disease, and corticosteroids are effective in emergency therapy and in chronic management of this disease.[9] Corticosteroids reduce inflammation by inhibition of phospholipase A, the enzyme responsible for the initial metabolism of arachidonic acid into inflammatory mediators. Corticosteroids also decrease migration of inflammatory cells into the airway, thereby decreasing the concentration of granulocyte products such as major basic protein and other eosinophil-derived products.

The duration and dose of corticosteroid therapy depend on the degree and chronicity of respiratory embarrassment in the cat, the severity of the pulmonary infiltrate, and the severity of inflammation on cytology. An individualized approach to antiinflammatory treatment is required for each case. Initially, prednisolone should be administered at 1 mg/kg PO q12h for 5 to 10 days, and the dosage decreased to 0.5 mg/kg q12h for 5 to 10 days if a good therapeutic response is seen. If the patient remains relatively free of respiratory signs, the dosage may be decreased over time to once-daily or every-other-day treatment. Recurrent episodes of coughing or respiratory distress necessitate a return to the original dosage. Repeat diagnostic testing also may be indicated. Cats are relatively resistant to the side effects of corticosteroids; however, an attempt should be made to achieve the lowest dose of the drug that will control signs. Approximately one half to two thirds of cats require lifelong medication.[9]

Cats that cannot be medicated orally can be treated with intramuscular injection of a repositol corticosteroid (methylprednisolone acetate at 10 to 20 mg IM every 2-8 weeks); however, this method provides only sporadic control of airway inflammation. Alternately, inhaled treatment can be prescribed. Both corticosteroids and bronchodilators are readily available from human pharmacies as metered dose inhalers (MDIs). Administration of inhaled medication requires use of an MDI attached to a spacer with facemask. Spacers are available from many respiratory supply companies including Respironics (Aerochamber; Cedar Grove, NJ), Trudell Medical (Aerokat; London, Ontario, Canada), and DVM Pharmaceuticals (Miami, FL). The spacer device causes generation of an aerosol cloud from the MDI that separates large particles from smaller particles, creating 1 to 7 micron particles that will deposit in airways during tidal respiration. In healthy cats, nebulization of a product administered via spacer and facemask resulted in adequate pulmonary deposition.[15] Investigations of pulmonary deposition of drug delivery from an MDI attached to a facemask or in cats with airway disease have not been performed, although clinically, this method has proven efficacious in controlling clinical signs in many cats.

Various preparations of antiinflammatory and bronchodilator medications are available for aerosol therapy via MDIs. The most commonly recommended steroid is Flovent (fluticasone propionate), which is available as an MDI containing 120 doses. Three strengths of drug are available: 220 µg/dose, 110 µg/dose, and 44 µg/dose. The 110-µg dose is used most commonly. The MDI must be shaken well before actuation and must be attached to the spacer before the dose is ejected. Typically, the MDI is actuated once per treatment, and the cat inhales 8 to 10 breaths (10 seconds) to deposit drug in the airways. Some of the side effects noted in human medicine include adrenal suppression with long-term and high-dose use, thinning of skin, and perioral dermatitis or infection (particularly with candidiasis). These complications have not been noted in veterinary patients.

In cats with moderate to severe clinical manifestations of disease, standard doses of oral steroids generally are recommended during the first several weeks of inhaled therapy, and the oral dose then can be tapered downward depending on clinical response.

For bronchodilation, an inhaler containing a β-agonist (Proventil or generic) can be given. The MDI contains 200 doses of 90 µg/dose or 108 µg/dose. When both bronchodila-

tors and steroids are given by inhalation, the bronchodilator is administered first, and the second drug can be given after 5 to 10 minutes.

Inhaled medications are more expensive than oral medications, but they may result in improved owner compliance, particularly when cats are difficult to medicate orally and chronic therapy is required. Many owners find that cats tolerate inhalation treatment readily, although problems may be encountered. Some cats may be frightened by actuation of the MDI, although they often become habituated to the sound with training. In an acute asthmatic attack, tolerance of the small facemask can be variable until the cat has learned to accept the device. An additional concern may be the competence of drug delivery because owners lack ability to deploy the device correctly, or because of a failure of the device to induce deposition of aerosol into constricted airways. It is unclear whether this is a concern in treatment of cats. Finally, breath-holding by the cat can be a reason for treatment failure.

Alternative antiinflammatory drugs may be beneficial in some cats. In an experimental model of feline asthma, cyproheptadine, a serotonin-receptor blocker, attenuated airway constriction of isolated bronchial strips in vitro.[16] Serotonin levels have not been measured in naturally occurring feline bronchial disease; however, some cats may benefit from administration of serotonin antagonists. Cyclosporine, an inhibitor of T lymphocyte activation, attenuates bronchoconstriction and airway remodeling in asthmatic human patients and in a feline model of airway hyperreactivity.[17] Because cyclosporine absorption and distribution are extremely unpredictable, blood levels must be measured weekly until the desired trough level is achieved. The variable pharmacokinetics of cyclosporine and the potential toxicity of the drug make other agents more suitable for first-line therapy of feline bronchial disease; however, it could be considered for cases that are nonresponsive to standard therapy.

Bronchodilators

Bronchodilators can be helpful in emergency situations, in chronic management, and in control of exacerbations of disease in cats with bronchial disease. In some cases, bronchodilators allow a reduction in the dose of corticosteroids required to control clinical signs. This would be especially beneficial in cats afflicted with chronic recurrent bacterial infections, immunodeficiency, or diabetes mellitus. Individual cats show variable response to different classes of bronchodilators. If the drug used initially does not improve the cat's clinical condition, an alternate class of drug should be employed. Adverse effects of bronchodilators include gastrointestinal upset, sinus tachycardia, and hyperexcitability.

β AGONISTS. Administration of a β_2 agonist results in bronchodilation resulting from direct relaxation of airway smooth muscle. Terbutaline currently is the recommended adrenergic agent for cats. Intravenous terbutaline has been shown to reduce airway resistance acutely in cats with constricted airways,[6] and pharmacokinetic studies have established the safety of the drug. The recommended dose is 0.01 mg/kg parenterally q12h to q6h or 0.625 mg PO q12h.[18] Theoretically, down-regulation of β-receptor density could occur with chronic use, resulting in decreased efficacy of the drug; however, this rarely is recognized clinically.

METHYLXANTHINES. Theophylline may provide some relief from clinical signs by preventing acute attacks of bronchoconstriction in predisposed cats, by suppressing inflammation, or by reducing the dose of corticosteroid required. Pharmacokinetics have not been established for sustained-release theophylline products currently on the market. Extrapolating from a dosage provided for dogs,[19] extended-release theophylline (Inwood Laboratories, Commack, NY) can be administered at a dosage of 10 mg/kg PO in the evening.

Other

Antibiotics should be prescribed based on culture/sensitivity and cytology results because airway infection may contribute to bronchial inflammation and hyperresponsiveness. If infection with *Mycoplasma* spp. is suspected, a clinical trial of doxycycline (3 to 5 mg/kg PO q12h) can be prescribed while cultures are pending. If parasitic infection with *Aleurostrongylus* spp. is documented or suspected as a cause for airway inflammation, fenbendazole can be administered at 50 mg/kg PO q24h for 10 days, or ivermectin can be used (300 µg/kg PO or SQ twice, 3 weeks apart).

PREVENTION

Feline airways are rich in sympathetic innervation, and β_2-adrenergic activation is important in providing bronchodilation. Therefore beta-blockers such as propranolol (a nonspecific beta blocker) and atenolol (primarily a β_1–blocker) should be avoided if bronchial disease is suspected. Atropine, although it is a potent bronchodilator, should not be used chronically in bronchial disease, because it thickens bronchial secretions and encourages mucus plugging of the airways.

Situations that might provoke bronchoconstriction should be avoided, particularly in cats that develop acute attacks of severe respiratory distress. Cigarette smoke, dusty litters, aerosol sprays, polluted environments, stressful situations, and exposure to upper respiratory viruses can trigger clinical signs in susceptible cats.

PROGNOSIS

Bronchial disease is a relatively common respiratory disease encountered in cats of all ages and various breeds. It is a chronic disorder, and cats often exhibit either chronic persistent signs or recurrent episodes of clinical disease. Therapy with antiinflammatory drugs and bronchodilators alleviates acute clinical signs in most cases; however, a significant proportion of cats suffer a recurrence or persistence of signs. In the absence of an identifiable cause of airway inflammation, the majority of cats with idiopathic bronchial disease require continuous medication throughout their lives.[9] Owners should understand the need for continual medical care and be encouraged to communicate closely with their veterinarian to provide individualized therapy.

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Chapter 40

CHYLOTHORAX

Theresa W. Fossum

Management of animals with chylothorax has been refined drastically since the initial report of its surgical treatment in three dogs and one cat in 1958.[1] However, our ability to treat affected animals effectively has been hindered by a lack of understanding of the etiology of this devastating disease. Appropriate treatment of affected cats depends foremost on confirmation of the diagnosis and identification of the cause. Once the diagnosis has been made and concurrent diseases have been ruled out, the value of medical versus surgical treatment must be considered.

EPIDEMIOLOGY

Although the prevalence of chylothorax is unknown, a recent survey of 2000 veterinary clinics regarding the diagnosis and treatment outcomes of dogs and cats presenting with chylothorax suggested that cats were diagnosed with chylothorax approximately four times more often than were dogs.[2] Of 795 veterinarians or veterinary centers returning the survey, nearly 40 per cent had diagnosed at least one dog or cat with chylothorax in a 5-year period, contributing information regarding 76 dogs and 297 cats with chylothorax.

ETIOLOGY AND PATHOGENESIS

Chylothorax previously was thought a result of thoracic duct rupture secondary to trauma; however, this is now known to be a relatively rare cause of chylothorax. Although traumatic rupture of the thoracic duct may occur, the thoracic duct heals spontaneously in most of these animals, and clinical signs associated with chylothorax are not recognized.[3,4] More commonly recognized causes in cats include mediastinal lymphosarcoma,[5] cardiomyopathy[6] (particularly secondary to hyperthyroidism), pericardial disease,[7] paroxysmal atrioventricular block,[8] fungal granulomas,[9] and heartworm infection.[10-12] Unfortunately, despite extensive diagnostic evaluation, the underlying etiology is undetermined (idiopathic chylothorax) in a majority of affected cats.[13,14] Because treatment of this disease varies considerably depending on the underlying etiology, clinicians must identify concurrent disease processes before definitive therapy is initiated.

Because any disease that results in high venous pressures (e.g., cardiomyopathy, pericardial effusion, congenital cardiac abnormalities, and heartworm disease) may cause chylothorax, a complete cardiac evaluation is warranted in affected cats. Treatment of cats with cardiomyopathy and chylothorax should be based primarily on palliation with thoracentesis when necessary and on improving cardiac output and decreasing venous pressures with appropriate drug therapy. If pericardial effusion is diagnosed, the underlying etiology should be determined and pericardiectomy performed, if indicated. Although heartworm infection is uncommon in cats, experimental infection with *Dirofilaria immitis* has been shown to result in chylothorax in a small number of cases.[10] Naturally occurring heartworm disease also has been associated with chylothorax in cats.[11,12] Therefore cats with chylothorax should be screened for heartworm infection (see Chapter 36).

If an anterior mediastinal mass is identified, a fine-needle aspirate may be performed to determine the tumor or tissue type. Specific therapy (i.e., radiation therapy, chemotherapy, antifungal therapy, surgery) then should be instituted according to findings. The chylous effusion probably is secondary to compression of the cranial vena cava by the mass in these animals, and shrinkage of the mass may result in resolution of the pleural fluid. For prognostic purposes, assessment of feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) status is prudent in affected cats. The pericardium is thickened in some patients with chylothorax, associated with chronic irritation induced by chyle.[15] The pericardial thickening may lead to elevated right-sided venous pressures. Abnormal venous pressures may act to impede the drainage of chyle via lymphaticovenous communications after thoracic duct (TD) ligation.

The term *idiopathic* chylothorax is used when no obvious underlying disorder can be found. Unfortunately, management of patients with idiopathic chylothorax is difficult. Until the etiology of chylothorax in these animals is understood, therapy remains palliative and less than optimal in many instances. One possibility is that these animals have increased volumes of lymph being transported through the thoracic duct. These increased flows may occur secondary to abnormal right-sided venous pressures that cause much of the lymph, normally transported from the liver into the venous system, to be shunted into

the lymphatic system. Minimally elevated venous pressures, in association with other unknown factors, may be sufficient to elevate lymphatic flows substantially through the thoracic duct.

CLINICAL SIGNS

Most cats with chylothorax present with a normal body temperature, unless extremely excited or severely depressed. Additional findings in patients with chylothorax may include muffled heart sounds, depression, anorexia, weight loss, pale mucous membranes, arrhythmias, murmurs, and pericardial effusion.

SIGNALMENT

Oriental breeds (i.e., Siamese and Himalayan) appear to have an increased incidence of chylothorax. Although chylothorax may affect animals of any age, older cats in one study were more likely to develop chylothorax than were young cats.[13] This finding was believed to indicate an association between chylothorax and neoplasia.

HISTORY

Coughing often is the first (and occasionally the only) abnormality noted by owners until the affected cat becomes dyspneic. Many owners report they first noticed coughing months before presenting the animal for veterinary care; therefore cats that cough and do not respond to standard treatment of nonspecific respiratory problems should be evaluated for chylothorax. Coughing may be a result of irritation caused by the effusion or may be related to the underlying disease process (i.e., cardiomyopathy, thoracic neoplasia).

DIAGNOSIS

Radiography and Ultrasonography

Patients that have collapsed lung lobes that do not appear to reexpand after removal of chyle or other pleural fluid should be suspected of having underlying pulmonary parenchymal or pleural disease, such as fibrosing pleuritis (Figure 40-1). Diagnosis of fibrosing pleuritis is difficult. The atelectatic lobes may be confused with metastatic or primary pulmonary neoplasia, lung lobe torsion, or hilar lymphadenopathy (Figure 40-2). Radiographic evidence of pulmonary parenchyma that fails to reexpand after removal of pleural fluid should be considered possible evidence of atelectasis with associated fibrosis. Fibrosing pleuritis also should be considered in cats with persistent dyspnea in the face of minimal pleural fluid.

Laboratory Findings

Fluid recovered by thoracentesis should be placed in an EDTA tube for cytological examination. Placing the fluid in an EDTA tube rather than a "clot-tube" allows performance of cell counts. Although chylous effusions are classified routinely as exudates, the physical characteristics of the fluid may be consistent with a modified transudate. The color varies, depending on dietary fat content and the presence of concurrent hemorrhage. The protein content is variable and often inaccurate because of interference of the refractive index by the high lipid content of the fluid. The total nucleated cell count usually is less than 10,000/µl and consists primarily of small lymphocytes or neutrophils, with lesser numbers of lipid-laden macrophages.

Chronic chylous effusions may contain low numbers of small lymphocytes because of the inability of the body to compensate for continued lymphocyte loss. Nondegenerative neutrophils may predominate with prolonged loss of lymphocytes, or if multiple therapeutic thoracenteses have induced inflammation. Degenerative neutrophils and sepsis are uncommon findings because of the bacteriostatic effect of fatty acids, but can occur iatrogenically as a result of repeated aspirations.

Pseudochylous effusion is a term that has been misused in the veterinary literature to describe effusions that look like chyle, but in which a ruptured TD is not found. Given the known causes of chylothorax in dogs and cats, this term should be reserved for effusions in which the pleural fluid cholesterol is greater than the serum cholesterol concentration and the pleural fluid triglyceride is less than or equal to the serum triglyceride. Pseudochylous effusions are extremely rare in veterinary patients but may be associated with tuberculosis.

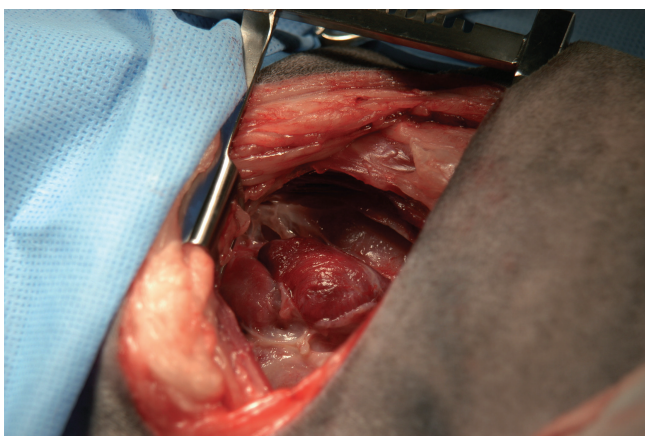

Figure 40-1. Photomicrograph of the lungs of a cat with fibrosing pleuritis associated with chylothorax. Notice the thickened pleura and the rounded appearance of the lung lobes.

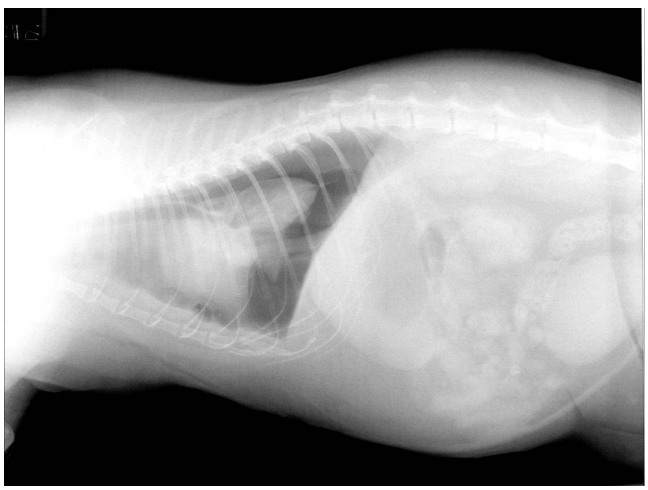

Figure 40-2. Lateral view of lungs of a dog with chronic chylothorax. Notice the severe atelectasis and shrunken appearance of the lung lobes.

DIFFERENTIAL DIAGNOSIS

Chylothorax must be differentiated from other types of pleural effusion. Pyothorax may appear grossly similar to chylothorax, but the predominant cell type is a degenerative neutrophil in patients with infection of the pleural space. To help determine if a pleural effusion truly is chylous, several tests can be performed including comparison of fluid and serum triglyceride levels; Sudan III stain for lipid droplets; and the ether clearance test. The most diagnostic test is comparison of serum and fluid triglyceride levels. Truly chylous effusion contains a higher concentration of triglycerides than serum collected simultaneously.

MEDICAL MANAGEMENT

If an underlying disease is diagnosed, it should be treated and the chylous effusion managed by intermittent thoracentesis. If the underlying disease is treated effectively, the effusion often resolves; however, complete resolution may take several months. Surgical intervention should be considered in cats with idiopathic chylothorax or in those that do not respond to medical management. Chest tubes should be placed only in those patients with suspected chylothorax secondary to trauma (very rare), when rapid fluid accumulation necessitates that thoracentesis be performed several times each week to prevent dyspnea, or after surgery. Electrolytes should be monitored, because hyponatremia and hyperkalemia have been documented in dogs with chylothorax undergoing multiple thoracenteses.[16] A low-fat diet may decrease the amount of fat in the effusion, which may improve the affected cat's ability to resorb fluid from the thoracic cavity.

Commercial low-fat diets are preferable to homemade diets; however, if commercial diets are refused, homemade diets are a reasonable alternative (Table 40-1; the fat content of these diets is about 6 per cent on a dry basis). Medium-chain triglycerides (once thought to be absorbed directly into the portal system, bypassing the TD) are transported via the TD of dogs. Therefore they may be less useful than believed previously. Additionally, they are relatively unpalatable and most cats refuse to eat food to which they have been added. Dietary therapy probably will not cure this disease, but it may help in the management of animals with chronic chylothorax. Clients should be informed that no effective treatment exists that will stop the effusion in all cats with the idiopathic form of this disease. However, the condition may resolve spontaneously in some patients after several weeks or months.

Benzopyrone drugs such as rutin have been used for the treatment of lymphedema in human beings for years and have been recommended for the treatment of chylothorax in cats. Although a small number of cats with chylothorax reportedly have resolved the effusion after treatment with this drug,[17,18] the efficacy of rutin in the treatment of this disease is unproven. The recommended dosage of rutin in cats is 50 to 100 mg/kg PO q8h.

Somatostatin is a naturally occurring substance with an extremely short half-life. It inhibits gastric, pancreatic, and biliary secretions (i.e., glucagon, insulin, gastric acid, amylase, lipase, and trypsin) and prolongs gastrointestinal transit time, decreases jejunal secretion, and stimulates gastrointestinal water absorption. In recent years, analogues of somatostatin have been used successfully to treat human beings with traumatic or postoperative chylothorax.[19,20] Reduced gastrointestinal secretions may aid healing of the thoracic duct in these patients by decreasing thoracic duct lymphatic flows. It also has been reported to result in early decreased drainage and early fistula closure in dogs with experimental transection of the thoracic duct.[21] The mechanism by which nontraumatic chylothorax may benefit from this treatment is unclear; however, resolution of pleural fluid has been reported in cats with idiopathic chylothorax in whom octreotide has been administered.[22] Octreotide (Sandostatin; 10 µg/kg SQ q8h for 2 to 3 weeks) is a synthetic analogue of somatostatin that has a prolonged half-life and minimal side effects. Soft stools that resolve after withdrawal of the drug may occur. Prolonged treatment should be discouraged, because treatment for longer than 4 weeks has been associated with gallstone formation in human beings. I have used octreotide in two dogs; one with chylothorax and one with serosanguinous effusion after TD ligation. Although the latter dog resolved the effusion within a few days of treatment, the former case did not respond. The efficacy of octreotide in animals with chylothorax warrants further investigation.

Table 40-1 | **Feline Homemade Low-Fat Diet***

INGREDIENT	AMOUNT
Cooked white rice	3⅔ cups
Stewed chicken	½ lb
Dicalcium phosphate†	1½ tsp
GNC Ca-Mg (600 mg Ca/tab)‡	1½ tab
Morton Lite Salt	1 tsp
Taurine tablets (500 mg taurine/tab)§	3 tabs
Zinc (50 mg zinc/tab)¶	½ tab
Feline Pet Tab	3 tabs
Radiant Valley Natural Selenium (100 mcg Se/tab)¶	½ tab
Nature Made Balanced B-50 Complex¶	½ tab
GNC Choline (250 mg choline/tab)‡	1 tab
DIRECTIONS	
Cook the rice without salt. Boil chicken and skim fat. Crush tablets to a fine powder. Combine all ingredients and mix well. Refrigerate unused portions.	

* Calculations based on average published nutrient content of each ingredient indicate this diet meets or exceeds the nutrient maintenance requirements for adult cats published by the Association of American Feed Control Officials. This recipe makes about 2¼ lbs of food that contains 1293 kcal of metabolizable energy.
† Dicalcium phosphate 18.5 per cent phosphorus, 22 to 24 per cent calcium, available at farm supply and feed stores.
‡ General Nutrition Corp., Pittsburgh PA, available at GNC Nutrition Centers.
§ Taurine tablets can be purchased at most health food stores and cooperatives as 500-mg and 1000-mg tablets.
¶ Available at many supermarkets or health food stores.

PATHOLOGICAL FINDINGS

Fibrosing pleuritis is a life-threatening complication of chronic chylothorax in cats. In addition to chylothorax, pyothorax, feline infectious peritonitis, hemothorax, and tuberculosis have been associated with the development of fibrosing pleuritis.[23] Although the cause of the fibrosis is unknown, apparently it can develop subsequent to any prolonged exudative or blood-stained effusion. Exudates are characterized by a high rate of fibrin formation and degradation. Fibrin formation probably increases because chronic inflammatory exudates, such as

chylothorax and pyothorax, induce changes in mesothelial cell morphological features, resulting in increased permeability, mesothelial cell desquamation, and triggering of both pathways of the coagulation cascade. These desquamated mesothelial cells also have been shown to produce type III collagen in cell culture, which promotes fibrosis. Additionally, the chronic presence of pleural fluid may lead to impairment in the mechanism of fibrin degradation. Fibrinolysis may decrease because direct injury to mesothelial cells may reduce inherent fibrinolytic activity of the cells, and/or the increased fluid volume may dilute local plasminogen activator. Plasminogen activator converts the precursor plasminogen to its active form plasmin. Fibrinolytic activity in mammals is attributable primarily to this serine protease. In animals with fibrosis, the pleura is thickened by diffuse fibrous tissue that restricts normal pulmonary expansion. Pulmonary function testing in human patients with fibrosing pleuritis has shown a decrease in vital capacity and static compliance, which necessitates greater negative intrapleural pressures for any given change in lung volume when compared with healthy patients.

SURGICAL TREATMENT

Surgical intervention is warranted in cats that do not have underlying disease and in which medical management becomes impractical; for example, when thoracentesis is required more frequently than once a week, or when repeat thoracentesis fails to relieve the dyspnea. Surgical options include mesenteric lymphangiography and TD ligation,[13,24,25] subtotal pericardiectomy,[15] omentalization,[26] passive pleuroperitoneal shunting,[27] active pleuroperitoneal or pleurovenous shunting,[28] and pleurodesis.[29-31] Of these, I recommend only the first two (TD ligation and pericardiectomy) as first-line therapies. Pericardiectomy also may treat effectively or even prevent the serosanguineous effusions that occur occasionally after TD ligation in some patients.

In a recent study, TD ligation and pericardiectomy were performed in 17 animals, and pericardiectomy alone was performed in an additional three animals that presented over a 5½-year period to one institution.[15] Nineteen animals presented for evaluation of idiopathic chylothorax (9 dogs, 10 cats), whereas one dog presented for serosanguineous pleural fluid after TD ligation that had been performed elsewhere. Clinical signs of pleural fluid resolved in 8 of 10 cats and 10 of 10 dogs after surgery. The overall success rate for surgical treatment of chylothorax (i.e., resolution of pleural fluid) in this study was 90 per cent (80 per cent in cats and 100 per cent in dogs). These data suggest that TD ligation in conjunction with pericardiectomy has a favorable outcome in animals with idiopathic chylothorax.

The only effective treatment for fibrosing pleuritis is decortication; however, the indications and value of decortication in animals are unknown. Decortication may give the best functional result when the pleuritis is of short duration and pulmonary parenchymal disease is minimal. In such cases, the thickened pleura is not firmly adherent to the underlying parenchyma and can be removed without damaging the underlying lung severely; however, pneumothorax is a common sequela and usually requires tube thoracentesis. Decortication in human beings carries a good prognosis if only one or two lobes are involved; however, when the fibrosis is diffuse, as occurs in many animals with chylothorax, a guarded prognosis is warranted even with effective decortication. When more than one lung lobe is decorticated, reexpansion pulmonary edema may occur and often is fatal. If decortication is successful, lung expansion and pulmonary function may improve over a 2-month to 3-month period.

In a recent study, several animals were reported to have severe fibrosing pleuritis, despite the owners' claims that the clinical signs had been of recent onset.[15] In that study, decortication was deemed necessary in two cats because the extent of the pleuritis was such that it was thought that respiratory distress may still be present after surgery, even if the pleural fluid resolved. Both of these cats developed severe pneumothorax and required prolonged intensive management of this condition. One cat was determined to have a tracheal rupture that healed spontaneously over a 2-week period. Neither cat developed reexpansion pulmonary edema after decortication; therefore decortication may be of value in animals with severe fibrosing pleuritis in which increased lung expansion is deemed important. Owners must be cautioned of the increased morbidity and mortality associated with this condition, particularly with the development of reexpansion pulmonary edema.

Duration of clinical signs appears to be a highly unreliable predictor of the success of surgery or the extent of fibrosing pleuritis in animals with chylothorax. Many owners simply do not recognize clinical signs of chylothorax until the disease is well advanced. In such patients, fluid production may be offset by fluid resorption for months and therefore clinical signs are mild until sufficient pleural thickening occurs that fluid resorption is diminished or eliminated completely. *Importantly, the degree of fibrosing pleuritis does not appear to warrant a poor prognosis in cats.* I have operated on cats with severe fibrosing pleuritis that appear clinically normal once the effusion stops.

Thoracic Duct Ligation with Mesenteric Lymphangiography

TD ligation is performed in cats from a left lateral intercostal thoracotomy or transdiaphragmatically. The mechanism by which this technique is purported to work is that after TD ligation, abdominal lymphaticovenous anastomoses form for the transport of chyle to the venous system. Therefore chyle bypasses the thoracic duct and the effusion resolves. Advantages of TD ligation are that if it is successful, it results in complete resolution of pleural fluid (as compared with palliative procedures described below) and may prevent fibrosing pleuritis from developing. The disadvantages include long operative time, which is problematic in debilitated animals; a high incidence of continued or recurrent chylous or nonchylous (from pulmonary lymphatics) effusion; and difficulty of performing mesenteric lymphangiography (particularly in cats).

Without mesenteric lymphangiography, complete ligation of the thoracic duct cannot be ensured; however, an experimental paper assessing lymphangiography in cats suggested this technique may not be uniformly successful in verifying complete ligation of the thoracic duct.[25] Additionally, some animals may form collateral lymphatics past the site of the ligature and thus reestablish thoracic duct flow. If chyle flow is directed into the diaphragmatic lymphatics, chylothorax may continue or recur.

For lymphangiography, food is withheld 12 hours before surgery. The left side of the thorax and abdomen, or just the abdomen if a midline celiotomy is being performed, is prepared for aseptic surgery. If a thoracic approach to the thoracic duct

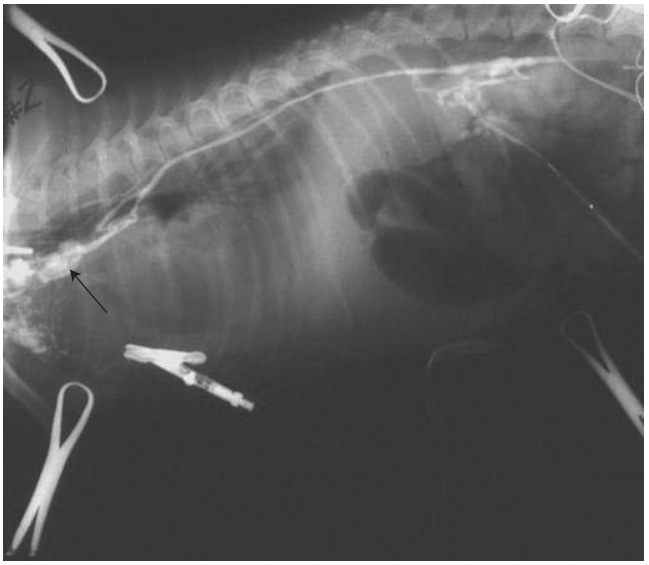

Figure 40-3. Lymphangiogram performed in a cat with chylothorax and thoracic lymphangiectasia. Note the multiple, dilated lymphatics near the entrance of the thoracic duct *(arrow)* into the venous system.

is being used, a left paracostal incision is made to exteriorize the cecum. Once the cecum has been exteriorized, a lymph node adjacent to the cecum is located. A small volume (0.1 to 1 ml) of methylene blue (USP 1 per cent, American Quinine, Shirley, NY) may be injected into the lymph node to increase visualization of lymphatics. Repeated doses of methylene blue should be avoided because of the risk of inducing a Heinz body anemia or renal failure. Careful dissection of the mesentery near this node allows large lymphatic vessels to be visualized and cannulated with a 22-gauge over-the-needle catheter. Cannulation of this lymphatic is more difficult in cats than in dogs because cats have more fat in their mesentery and their lymphatics are significantly smaller. Two sutures (4-0 silk) are placed in the mesentery and used to secure the catheter and an attached piece of extension tubing in place (the ends of the suture can be looped over the hub of the extension tubing). An additional suture may be placed around the extension tubing and through a segment of intestine to prevent dislodgement of the catheter. A three-way stopcock is attached to the end of the extension tubing and a water-soluble contrast agent is injected at a dosage of 1 ml/kg diluted with 0.5 ml/kg of saline. A lateral thoracic radiograph is taken while the last milliliter is being injected. This lymphangiogram can be used to help identify the number and location of branches of the thoracic duct that need to be ligated, and it can be repeated after ligation to help determine the extent of lymphangiectasia present in the cranial thorax (Figure 40-3).

The thoracic duct in cats typically is approached through a left caudal intercostal thoracotomy (eighth, ninth, or tenth intercostal space) or via an incision in the left diaphragm. Once the duct has been located, hemostatic clips can be used to ligate it. The advantage of using hemoclips (Edward Weck and Co. Inc., Research Triangle Park, NC) is that they can be used as a reference point on subsequent radiographs if further ligation is necessary. However, I prefer also to place a nonabsorbable suture, such as silk, on the duct. Visualization of the thoracic duct can be aided by injecting methylene blue into the lymphatic catheter (Figure 40-4). If a catheter was not placed, the dye can be injected into a mesenteric lymph node. Pericardiectomy may be performed from the same intercostal thoracotomy in most patients. If the pericardium cannot be reached, a second, more cranial, intercostal thoracotomy may be necessary.

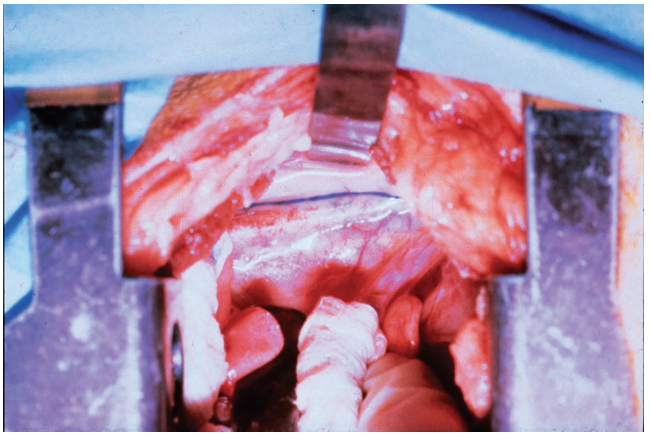

Figure 40-4. Identification of the thoracic duct can be aided by injecting methylene blue into the lymphatic catheter or directly into a mesenteric lymph node.

Active Pleuroperitoneal or Pleurovenous Shunting

Active pleuroperitoneal or pleurovenous shunting (Denver double valve peritoneous shunt, Denver Biomaterials Inc., Evergreen, CO) has been recommended for the treatment of chylothorax in dogs and cats and may be a reasonable consideration in patients in which all other therapies have failed.[28] Commercially made shunt catheters are available and can be used to pump fluid from the thorax to the abdomen. Under general anesthesia, a vertical incision is made over the middle of the fifth, sixth, and seventh ribs. A purse-string suture is placed in the skin at this site, and after the placement of fenestrations in the venous end of the shunt catheter, the catheter is inserted bluntly into the pleural space. A tunnel is created by blunt dissection under the external abdominal oblique muscle, and the pump chamber is pulled through the tunnel. The efferent end of the catheter then is placed into the abdominal cavity through a preplaced purse-string suture and incision located just caudal to the costal arch. The shunt must be placed with the pump chamber directly overlying a rib so that the chamber can be compressed effectively (Figure 40-5). Complications associated with pleuroperitoneal or pleurovenous shunts include (1) the shunts are expensive, (2) they may occlude easily with fibrin, (3) some animals will not tolerate compression of the pump chamber, and (4) the shunts require a high degree of owner compliance and dedication. Additionally, thrombosis, venous occlusion, sepsis, and electrolyte abnormalities have been reported in human patients.[32-34]

Omentalization

Omentalization has been reported as a technique to treat animals with chylothorax when other surgical treatments are not successful or deemed impossible.[26] A fifth or sixth space intercostal thoracotomy is made to provide access to the cranial

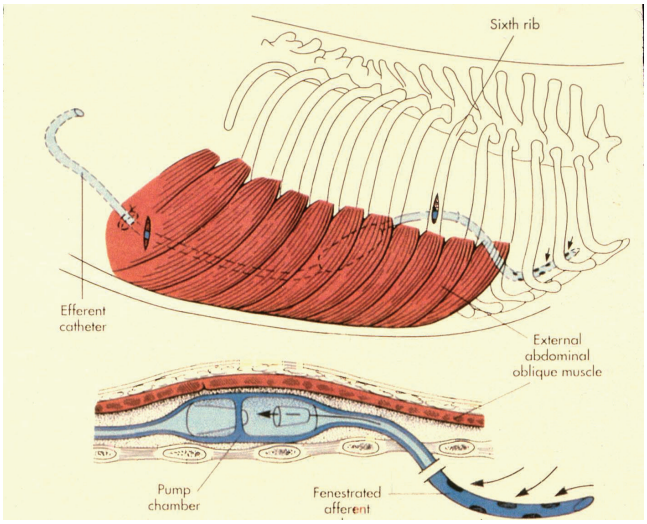

Figure 40-5. Diagram depicting placement of a pleuroperitoneal shunt. The pump chamber should be positioned over a rib so that it can be compressed manually. (From Fossum TW, editor: Small animal surgery, St Louis, 2002, Mosby.)

thorax. A paracostal incision then is made so that a dorsal omental pedicle flap can be raised. The omental flap is brought through an incision in the pars costalis of the diaphragm. Care should be taken to avoid rotation of or excessive tension on the omental pedicle. The omentum is spread out within the thorax to provide a large surface area. An omentopexy is performed by using synthetic absorbable suture to anchor the omentum to the mediastinum in the region of the lymphaticovenous anastomoses between the thoracic duct and the cranial vena cava. Sutures should be placed so that they do not interfere with the blood supply of the omentum. The success of this technique is unproven, and I do not recommend it routinely.

OTHER TREATMENTS

Passive pleuroperitoneal shunting has been recommended as treatment of chylothorax in cats, but I no longer recommend this technique. The goal of placing a fenestrated Silastic sheet in the diaphragm was to allow drainage of the chylous fluid into the abdomen where the fluid could be reabsorbed by visceral and peritoneal lymphatics and thereby alleviate the respiratory distress and need for subsequent thoracentesis.[18] I have not found this technique to be effective, and chronic irritation of the sheeting may be associated with neoplastic transformation of tissues.

Pleurodesis is the formation of generalized adhesions between the visceral and parietal pleura. Adhesions may occur spontaneously in association with pleural effusion, or they can be induced in some species after instillation of an irritating substance into the pleural cavity.[29-31] This technique has been recommended for the treatment of chylothorax in dogs and cats, but I do not recommend it. For pleurodesis to occur, the lungs must be able to contact the body wall; however, many patients with chronic chylothorax have some thickening of their visceral pleura, which prohibits normal lung expansion (see earlier discussion on fibrosing pleuritis). Neither mechanical (surgical) pleurodesis nor talc administration resulted in pleurodesis in experimental dogs; however, thickening of the pleura did occur in some animals.[31] Chemical or surgical pleurodesis is unlikely to be successful in cats with chylothorax.

SUMMARY

Chylothorax is a complex disease with many identified underlying causes including cardiac disease, mediastinal masses, heartworm disease, and trauma. Management of this disease should be directed at identification of the cause, if possible, and treatment of the underlying disorder. In cats with idiopathic chylothorax, medical management is recommended initially because the condition may resolve spontaneously. Owners should be aware of the potential development of fibrosing pleuritis in affected animals. When medical management is impractical or unsuccessful, surgical intervention should be considered. Surgical options include mesenteric lymphangiography and TD ligation, pericardiectomy, omentalization, passive pleuroperitoneal shunting, active pleuroperitoneal or pleurovenous shunting, and pleurodesis. Of these, I prefer only TD ligation and pericardiectomy because if successful, the result is complete resolution of the chylothorax, thereby reducing the risk of developing fibrosing pleuritis. Until the etiology of the effusion in cats with idiopathic chylothorax is understood, the treatment success rate will be less than ideal. Future research should be directed at determination of the pathophysiological mechanisms underlying this disease in cats.

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Chapter 41

Acute Ureteral Obstruction

Julie R. Fischer

Acute ureteral obstruction (AUO) is an emerging feline disease process[1-3] that can result rapidly in life-threatening electrolyte and metabolic derangements. All ages and breeds of cats seem susceptible, and AUO has been documented in previously nonazotemic cats and cats with preexisting azotemia or with nonazotemic urinary disease (e.g., urolithiasis). AUO currently is the most common cause of presentation of cats for hemodialysis (HD).[2,3] Successful short-term and long-term management of AUO depend on rapid diagnosis, proactive medical and/or surgical care, thorough client education, and meticulous patient follow-up and management. Maintaining a high index of suspicion for AUO in an acutely uremic cat is critical to identification of this patient population and institution of appropriate care in a timely fashion (see Chapters 43, 44, and 46).

ETIOLOGY

Feline AUO usually results from intraluminal stones but also can occur secondary to nonmineralized intraluminal substances,[4] ureteral stricture,[5] surgical ligation or trauma,[6] mural or retroperitoneal neoplasia, and retroperitoneal fibrosis,[7] among other less common causes.[5]

Mineralized Obstructions

The most common cause of feline AUO is ureterolithiasis[8,9] and by far the most common urolith type identified in the feline upper urinary tract is calcium oxalate. Calcium oxalate is an insoluble mineral, and its prevalence in uroliths recovered from the canine and feline urinary tract has been increasing over the last decade. Currently, calcium oxalate is the chief component of more than 90 per cent of canine and feline nephroliths and ureteroliths.[1,10,11] These stones form in the kidney and sometimes pass into the ureter. Stones may be propelled successfully via ureteral peristalsis into the urinary bladder or may become lodged in the ureter along the way (Figure 41-1). Obstruction of the ureter increases ipsilateral ureteral peristaltic activity significantly, which can result in severe pain (ureteral colic).[2,12-14] Management of calcium oxalate uroliths in the feline urinary tract is discussed in detail in Chapters 43 and 46.

Nonmineralized Obstructions

AUO resulting from hardened clots of blood also has been documented in cats.[4] This type of obstruction can occur unilaterally or bilaterally and may consist of a single larger stonelike clot or many small ones. Causes of the blood accumulation are unknown, but prognosis and clinical course for these cats do not appear to be different from those of cats with mineralized obstructions. Ureteral trauma (e.g., trauma induced by stone passage) can cause a fibrinohemorrhagic exudate that may result in ureteral obstruction. Sloughed tissue and other debris from pyelonephritis also can collect in the renal pelvis and proximal ureter and obstruct urine flow.[4]

Ureters may be ligated inadvertently during ovariohysterectomy[6] (Figure 41-2) or other caudal abdominal surgery, or compressed, entrapped, or crushed by closure of a cystotomy incision located near the trigone. Surgical damage to the ureters often is not noted before development of severe uremia and hyperkalemia, and surgical revision is required for resolution. The normal feline ureteral lumen has an internal diameter of approximately 0.4 mm[5,15]; therefore its patency can be disrupted easily by inflammation or fibrosis from any cause. Surgical manipulation of the ureters must be performed in a fashion that minimizes the effect of this inevitable postsurgical swelling and the ensuing fibrosis associated with healing, lest the surgery itself result in ureteral obstruction. Surgical techniques to address ureteral obstruction are discussed briefly below.

Primary ureteral neoplasia occurs but is rare; more often, ureteral obstruction resulting from neoplasia occurs secondary to trigonal tumors. Bladder cancers are rarer in cats than in dogs, but primary trigonal tumors, most often transitional cell carcinoma, smooth muscle tumor, or lymphoma, do occur in cats[16] and can cause bilateral ureteral obstruction and an acutely uremic presentation.

EPIDEMIOLOGY AND DISEASE PROGRESSION

In a recent review, the median age of 50 cats with AUO managed with hemodialysis was 6 years, with a range of 8

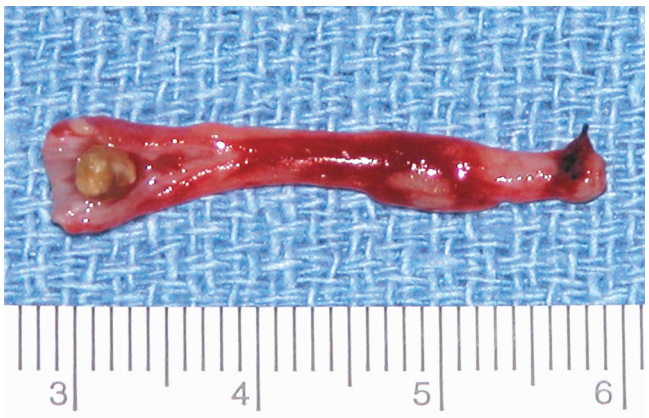


Figure 41-1. A resected segment of feline ureter with a 2-mm to 3-mm diameter obstructive calcium oxalate urolith present in situ.

Table 41-1 | **Selected Clinical and Clinicopathological Data from 50 Cats Presented for Dialytic Management of Acute Ureteral Obstruction**

PARAMETER	MEDIAN (RANGE)
Age (years)	6 (1-16)
Body temperature (°C)*	37.5 (34.2-39.1)
BUN (mg/dl)*	238 (68-456)
Creatinine (mg/dl)*	17.4 (8.4-34.4)
Potassium (mmol/l)*	6.8 (2.1-10.9)
Systolic blood pressure (mm Hg)*	142 (86-220)
Number of HD treatments	3 (1-8)
Phosphorus (mg/dl)*	15.6 (1.1-27.6)

*Value at presentation for hemodialysis (HD).

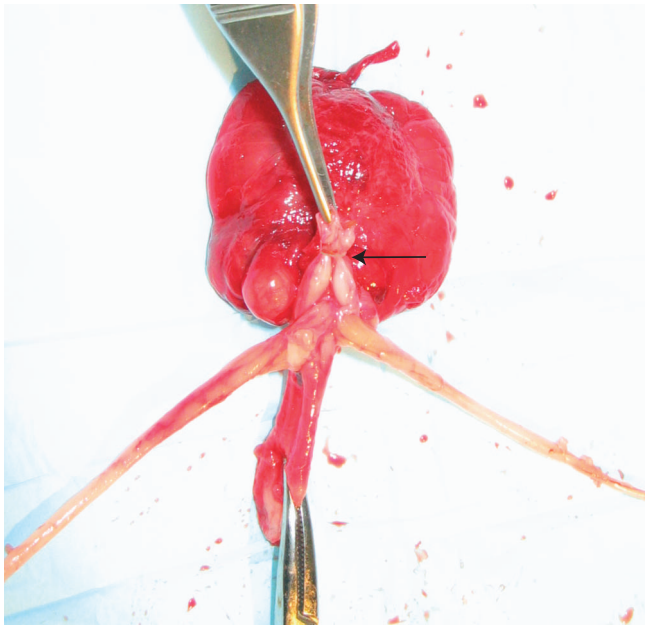
months to 16 years.[2] No sex predilection was identified, but Siamese cats appeared overrepresented.[17] Cats were markedly azotemic and many were hyperkalemic. Additional clinical and clinicopathological data associated with this series of cats are presented in Table 41-1.

Obstruction of one or both ureters initiates a complex cascade of events, which eventually can result in permanent loss of function in the associated kidney(s).[18] The exact course of events varies depending on age, species, degree of obstruction, and whether one or both ureters are obstructed.[18,19] A brief overview of the pathophysiology of complete, unilateral ureteral obstruction (CUUO) follows; unless specified otherwise, events described refer to the kidney ipsilateral to the obstruction.

CUUO (as with ureteral ligation or ureterolithiasis) causes an increase in ureteral pressure, which results in a nearly immediate increase in proximal tubular pressure. Renal blood flow and ureteral pressure increase initially.[20]

A concurrent increase in glomerular capillary hydrostatic pressure occurs, but not in proportion to the increase in tubular pressure. Because of this change, the net hydrostatic pressure gradient across the glomerular capillaries decreases, resulting in a decline in filtration (decreased glomerular filtration rate [GFR]).[21]

After 5 to 6 hours, intratubular pressures start to decline (and are back at preobstruction levels by 24 hours), but glomerular capillary pressures decline faster, so GFR stays significantly decreased or absent. After 24 hours of obstruction, the decreased



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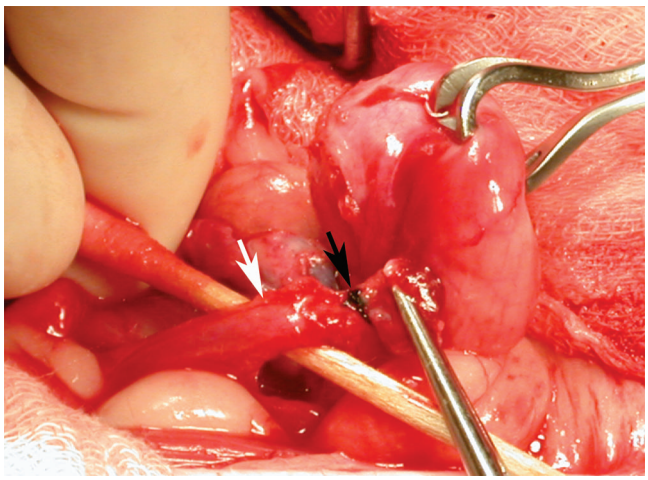


B

Figure 41-2. Two examples of inadvertent ureteral ligation during ovariohysterectomy. **A,** The horns of the uterus have been ligated together, encircling and entrapping the bladder neck, compressing the ureterovesical junctions and causing the ureters to be directed caudally. The *solid black arrow* indicates the ligature around the two uterine horns. The urethra and vagina are being retracted caudally. The bladder *(top)* is markedly congested and edematous. **B,** The ureters have been ligated individually by transfixation suture to the uterine stump. The *solid black arrow* indicates the suture transfixing the right ureter to the uterine stump. The *solid white arrow* indicates the fluid-distended right ureter cranial to the ligature. The bladder is reflected caudally with tissue forceps. (Photo courtesy Joshua Jackson.)

GFR in the obstructed kidney induces a compensatory increase in GFR in the contralateral normal kidney.[22]

Prostaglandin release causes renal blood flow to increase transiently to the cortex (and decrease to the medulla), but then afferent arteriolar resistance begins to increase, resulting in decreased GFR. In a study examining normal, conscious dogs subjected to CUUO via ligation, GFR in the obstructed kidney decreased to 50 per cent of controls at 24 hours, 30 per cent after 6 days, 20 per cent after 2 weeks, and 12 per cent after 8 weeks of obstruction.[23]

Events that lead to the long-term development of interstitial fibrosis are initiated promptly after obstruction. In rabbit models of complete ureteral obstruction, increased presence of renal interstitial collagen fibers is detectable by 7 days post obstruction, and organized interstitial fibrosis and tubular basement membrane thickening are detectable microscopically by 16 days post obstruction.[24,25]

The degree of permanent renal damage resulting from ureteral obstruction depends on the completeness and duration of obstruction. Irreversible damage actually occurs more rapidly, and recovery of function is slower when a normal contralateral kidney is present than when bilateral obstruction occurs.[18] Prospective studies in cats have not been performed; most data regarding the consequences of ureteral obstruction are derived from other animal models. In one experimental study of normal dogs, near-complete return of renal function followed relief of CUUO that lasted 4 days.[26] After obstruction of 14 days' duration in dogs, 46 per cent of preobstructed function returned by 4 months post obstruction.[27] Urine concentrating ability may take months to return in the affected kidney or may never return. Concentrating ability can be regained fully after short-term (<1 week) obstruction; however, permanent damage to concentrating ability results after 4 weeks of obstruction.[21] The result of chronic CUUO is either severe interstitial fibrosis and an end-stage kidney or severe hydronephrosis and a fluid-filled shell of a kidney.

PATHOGENESIS

Clinical AUO often is a situation of *sequential bilateral* ureteral obstruction, with one ureter chronically obstructed and one ureter acutely obstructed. The typical progression of the disease is depicted in Figure 41-3. Initial unilateral ureteral obstruction rarely results in clinically apparent disease. The obstructed kidney enlarges at first because of hydronephrosis and interstitial edema but then begins to fibrose and atrophy with chronicity of obstruction; simultaneously, the contralateral kidney hypertrophies to compensate for the decrease in GFR. The disease remains clinically silent until the ureter associated with the hypertrophied kidney becomes obstructed, at which point uremia, often severe, occurs. A similar scenario is encountered in cats with a sole or primary functioning kidney that becomes obstructed. The pathogenesis of calcium oxalate urolithiasis, the most common cause of AUO, is discussed in Chapter 43.

CLINICAL SIGNS

The most dramatic clinical signs associated with AUO usually are the signs related to uremia, including anorexia or inappetence, lethargy, weight loss, fetid breath, and sometimes vomiting.[9] Owners may suspect abdominal discomfort or detect decreased or absent urination. The severe, acute "renal colic" associated classically with unilateral ureteral obstruction and ureteral spasm in human beings is appreciated rarely in cats. On physical examination, most cats presented for AUO do exhibit abdominal pain, however, localized to the obstructed kidney(s). The most likely source of discomfort is distention and stretching of the richly innervated renal capsule by pelvic distention and renal parenchymal edema.[18]

Cats with AUO may be polyuric, oligoanuric, or produce normal urine volumes depending on the degree of obstruction. In cases with sequential obstruction, the ureter associated with the end-stage kidney often is at least partially patent. This kidney may produce surprisingly large amounts of poor-quality urine that does little to mitigate azotemia but provides enough excretory function to prevent hyperkalemia and volume overload.

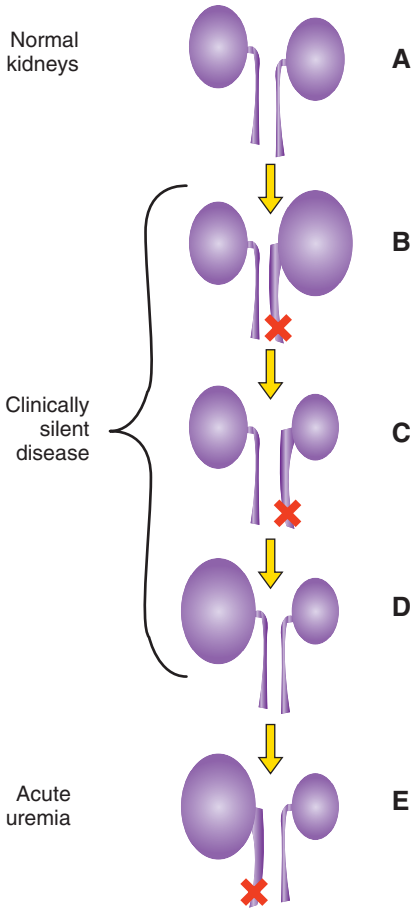


Figure 41-3. Schematic representation of progressive sequential ureteral obstruction. **A,** Kidneys and ureters are normal bilaterally. **B,** Obstruction of one ureter acutely results in slight enlargement of the corresponding kidney and possible dilation of the corresponding ureter. Disease often is clinically silent at this point. **C,** Over time, ureteral obstruction results in fibrosis and atrophy of the corresponding kidney. **D,** Simultaneously, the contralateral kidney hypertrophies to compensate for the decrement in overall renal function. **E,** Obstruction of the ureter associated with the hypertrophied kidney results in acute, often marked, uremia.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses for AUO include most other causes of feline acute uremia, including acute pyelonephritis, nephrotoxicoses (e.g., lily, ethylene glycol, nonsteroidal antiinflammatory medications), and renal lymphoma. Moderate to marked (>4 mm) renal pelvic and/or ureteral dilation, with or without renal asymmetry, renders AUO the most likely diagnosis.

DIAGNOSIS

Physical Examination

The mental status and general appearance of cats presented with AUO ranges from bright and interactive to moribund;

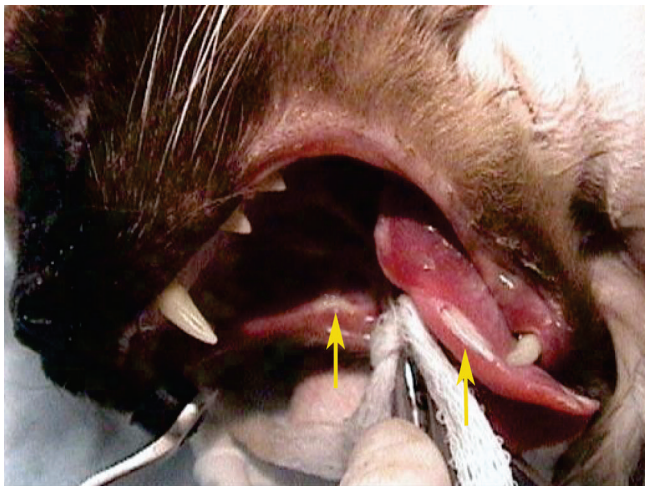


Figure 41-4. Uremic ulceration of the buccal mucosa and the ventrolateral margin of the tongue *(yellow arrows)* in a cat with AUO.

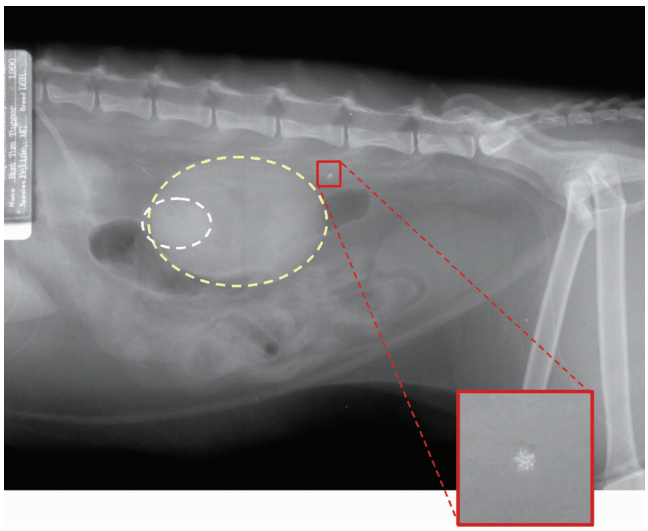


Figure 41-5. Lateral abdominal radiograph of a cat with AUO. Findings include one small kidney *(white oval)* and one dramatically enlarged kidney *(yellow oval)*. Scrutiny of the retroperitoneal space reveals a mineral opacity *(red box and enlarged inset),* strongly suggestive of a calcium oxalate ureterolith.

indeed, even some extremely azotemic cats (BUN >300 mg/dl) appear remarkably normal at first presentation. Most severely azotemic (BUN >100 mg/dl) cats are hypothermic (rectal temperature <37.8°C). A rectal temperature higher than 37.8°C in a cat with severe azotemia should be considered suspicious and should alert the clinician to the potential presence of concurrent infectious or inflammatory disease.

Careful initial assessment of hydration is critical, particularly if fluid therapy has been instituted already, because many AUO cats are oligoanuric and easily become overhydrated. Because uremic toxins can cause xerostomia, dry mucous membranes alone should not be taken as an indication of dehydration. Skin turgor correlates more reliably with hydration status in uremic patients. The breath odor often has a characteristic "uremic" quality (fishy, metallic, or ammoniacal) and also may smell necrotic if oral ulceration is present. Oral ulcers may not be readily apparent on examination of a nonsedated cat, because characteristic locations for these lesions are the ventrolateral lingual surfaces, the palatoglossal arches, and the buccal mucosa (Figure 41-4). The dorsal lingual surface also is affected commonly, particularly the tip of the tongue, which may ulcerate or fully necrose. A fundic examination should be performed with the cat's eyes properly dilated to detect retinal hemorrhages or detatchments, particularly if hypertension is documented. Altered pupillary light reflexes or menace reflexes may reflect cerebral damage from hypertension or uremia.

Significant renal asymmetry is common in cats with AUO and, if present, should raise suspicion of ureteral obstruction substantially. In some cats, the chronically obstructed kidney is so small that it cannot be found on abdominal palpation. The smaller kidney often is very firm and irregular. Most cats presented with AUO have some degree of palpable unilateral or, less commonly, bilateral renomegaly, and the enlarged kidneys usually are painful and have a resilient, turgid feel. Overhydration may result in peritoneal effusion, but effusion volumes usually are small.

No cardiopulmonary changes are specific to AUO; associated abnormalities are referable to severe uremia (e.g., pneumonitis, tachypnea), hyperkalemia (e.g., cardiac arrhythmias), volume overload (e.g., pulmonary edema, pleural effusion, gallop rhythm), and anemia (e.g., tachycardia, cardiac murmur).

Severe uremia and hyperkalemia can cause neurological abnormalities ranging from hyperreactivity to slight obtundation to seizure and coma. Additionally, many cats with AUO are hypertensive and have some degree of uremic platelet dysfunction, which can lead to significant cerebral hemorrhage. Again, these signs are sequelae to the uremic syndrome in general and are not specific to AUO.

Imaging Studies

Survey abdominal radiography may be the most sensitive, readily available diagnostic tool for detection of ureterolithiasis. Careful scrutiny of the retroperitoneal space often reveals tiny mineral opacities more difficult to visualize with ultrasound (Figure 41-5). Survey radiographs also allow comparison of kidney size and usually demonstrate nephrolithiasis if present.

The chronically obstructed kidney often is small, hard, and irregular on abdominal palpation and appears sonographically as an end-stage kidney. Evidence of obstruction (e.g., a ureterolith or hydronephrosis) may or may not be detected. The acutely obstructed kidney usually is normal to large in size, painful, and resilient on palpation. Ultrasonographically, renal parenchymal architecture may be relatively normal or may show evidence of chronic change (e.g., blurring of the corticomedullary junction or small cortical infarctions). The renal pelvis and/or ureter may be dilated to varying degrees.

The normal, nondilated renal pelvic space and ureter usually are not visualized with ultrasound; however, even slight (1-mm to 2-mm) dilation in the renal pelvis is detectable by a skilled operator.[28,29] Ureteral dilation may be more challenging to detect, depending on degree and location of the dilated segment. Dilation of the ureter and/or renal pelvis usually is apparent ultrasonographically within 3 to 4 days of obstruction (Figure 41-6). Documentation of moderate to marked (4 mm or less) renal pelvic and/or ureteral dilation can confirm suspicion of unilateral or bilateral ureteral obstruction rapidly, although

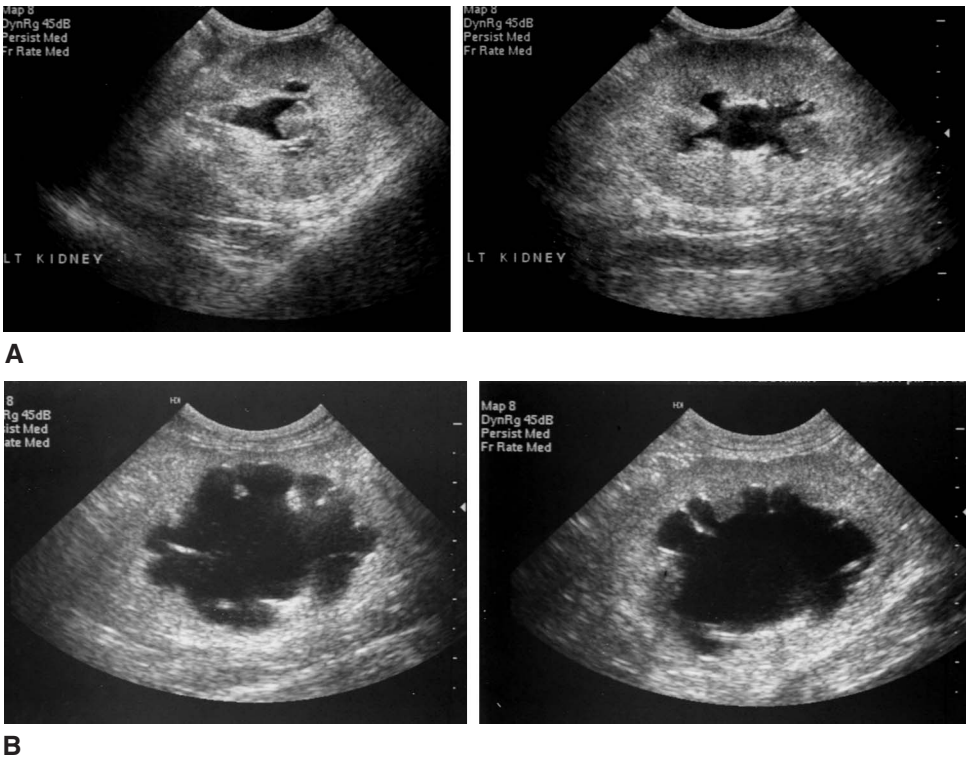


Figure 41-6. A, Transverse and longitudinal ultrasonographic images of a kidney with mild-to-moderate hydronephrosis secondary to AUO. Proximal hydroureter is seen in the transverse image. **B,** Longitudinal ultrasonographic image of a kidney with severe hydronephrosis secondary to ureteral obstruction.

the sonographic appearance does not confirm complete obstruction. Mild to moderate (less than 4 mm) renal pelvic or ureteral dilation can be consistent with obstruction or with pyelonephritis/ureteritis.

AUO results in a significant pressure increase in the renal pelvis, which causes compression of the renal parenchyma within the relatively noncompliant renal capsule. This increase in parenchymal pressure increases resistance to afferent blood flow in the kidney, a measure that can be assessed via Doppler ultrasonography. Measurement of the resistive index (calculated resistance to blood flow through the arcuate arteries) gives high diagnostic sensitivity and specificity in human beings for the differentiation of early ureteral obstruction from other causes of renal pain.[30,31] Resistive index has been evaluated in sedated normal dogs and cats[32,33] and in a small number of dogs and cats with obstructive and nonobstructive renal disease.[34] In this initial study of diseased animals, increase in resistive index was not a reliable sole determinant of the presence of obstructive renal disease, but the number of subjects was very small.[28] Increased familiarity with this technique and with its utility as an adjunctive diagnostic modality may permit more accurate, early, noninvasive identification of AUO.

Precise localization of the site of ureteral obstruction before surgery usually requires contrast radiography or computed tomography (CT); the *percutaneous antegrade pyelogram* provides rapid, cost-effective presurgical localizing information.[4,8] This study, performed under heavy sedation or general anesthesia, entails insertion of a long needle (e.g., 25-gauge to 22-gauge, 1½-inch to 3½-inch spinal needle) perpendicular to the renal capsule and into the dilated renal pelvis with ultrasound guidance. A small-volume T-port adaptor with a 6-ml syringe attached is connected to the spinal needle, and urine is withdrawn slowly from the renal pelvis until it is half to completely empty. Depending on degree of pelvic distension, less than 1 ml or more than 5 ml may be aspirated. Urine aspirated should be submitted for cytological analysis and bacterial culture. The syringe and T-port then are disconnected carefully from the spinal needle (which is held in place firmly by the operator) and replaced with another syringe and T-port, prefilled with a sterile, iodinated contrast medium such as diatrizoate (Renografin, Squibb, Princeton, NJ) or iopamidol (Isovue, Squibb, Princeton, NJ). A volume of contrast agent approximately equal to the volume of urine removed is injected slowly into the renal pelvis, until the operator feels a subjective increase in resistance. The emptying and filling processes may be monitored sonographically. When the filling is complete, the needle is removed carefully from the kidney, and serial lateral and ventrodorsal projection radiographs are performed (e.g., at 0, 5, 15, and 30 minutes). The degree of renal pelvic dilation usually is readily apparent, as is the site of ureteral obstruction (Figures 41-7 and 41-8). Leakage of contrast from the renal pelvis into the abdomen obscures visualization occasionally.[8]

Percutaneous antegrade pyelography also can diagnose AUO definitively in cats with mild to moderate upper tract dilation, although the smaller the renal pelvic dilation, the greater the operator skill required to perform the study safely. Other authors have pointed out the loss of antegrade pressure and potential drawbacks of antegrade pyelography when medical management of ureteral obstruction is anticipated (see Chapter 43).

Excretory urography (EU) is of limited diagnostic benefit in ureteral obstruction. Because of the significantly decreased

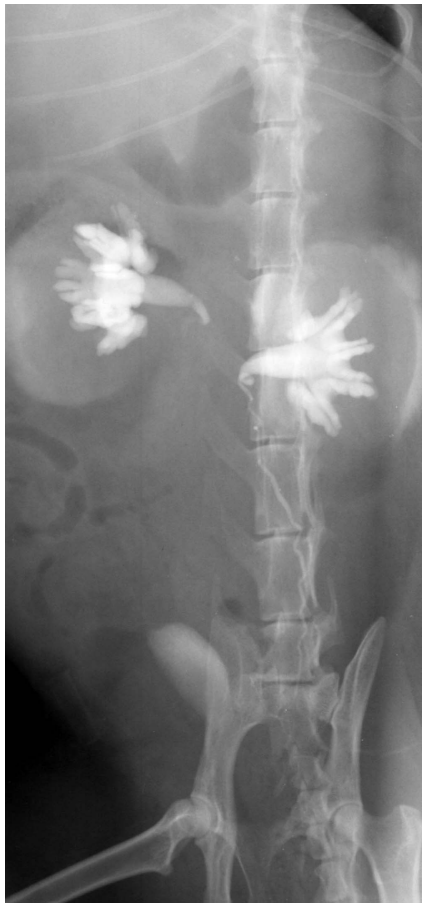
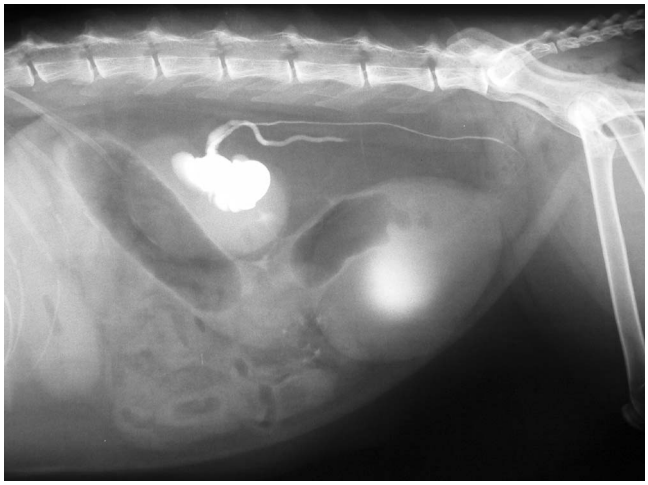


Figure 41-7. Obliqued ventrodorsal abdominal radiograph of a bilateral percutaneous antegrade pyelogram (20 minutes post injection). Bilateral moderate renal pelvic dilation and sharp demarcation of the calyces (particularly on the left) are present. The right ureter is markedly dilated proximally but tapers abruptly, and filling terminates 2 to 3 cm from the pelvis, which indicates proximal obstruction. The left ureter also is markedly dilated proximally and abruptly tapering, but contrast is observed along the length of the ureter and within the bladder, which indicates partial left ureteral patency or very recent resolution of obstruction. Note that renal size and margination are relatively normal bilaterally, which suggests *acute bilateral* rather than sequential obstruction.



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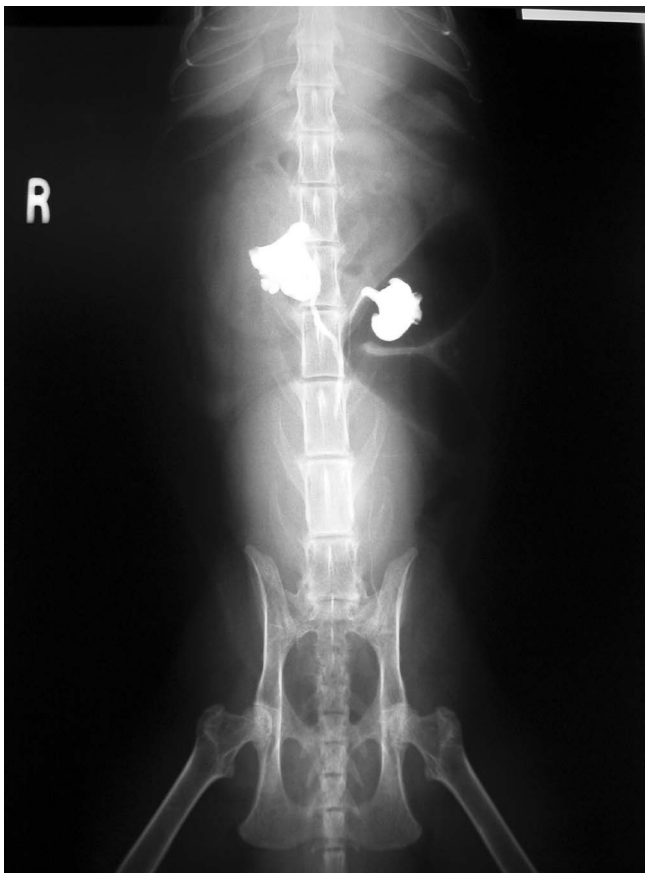

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Figure 41-8. Percutaneous antegrade pyelogram provided for contrast with Figure 41-7. Again, renal pelvic dilation is present bilaterally (and is marked) and one ureter is at least partially patent to the bladder, but loss of medullary architecture has occurred, which suggests chronicity and pressure atrophy. Note the marked renal asymmetry visible on the ventrodorsal projection (R>>L), strongly suggesting *sequential* rather than acute bilateral obstruction.

renal blood flow, reduced or absent glomerular filtration, and high pressure within the affected renal pelvis, concentration of contrast material and resulting opacification of the obstructed kidney and ureter are compromised. Studies in obstructed individuals may not have sufficient diagnostic value when planning appropriate intervention. Additionally, caution should be exercised in the administration of intravenous contrast materials to patients with preexisting renal compromise. Although the frequency of adverse effects is unknown in veterinary species, ample human data document a high risk of intravenous contrast-induced acute renal failure in patients with underlying chronic nephropathy.[35,36] When percutaneous antegrade pyelography is not available, however, EU may provide adequate presurgical localizing information and may be of more benefit than risk.

Helical computed tomography (CT) is the imaging diagnostic test of choice in many human hospitals for localizing ureterolithiasis and also is a very sensitive method of localizing mineralized obstructions in feline ureters.[5] In one prospective human study comparing helical CT and resistive index, sensitivity and specificity of helical CT and resistive index measurement were high for differentiation of obstructive nephropathy, with no statistical difference found between the diagnostic abilities of the two modalities.[30] Diagnostic

sensitivity of CT for nonmineralized ureteral obstructions in cats may be enhanced by performing excretory CT with intravenous iodinated contrast material.[5]

During administration of intravenous contrast material to a patient with renal compromise, adequate hydration is paramount.[37] Previous investigations have suggested that the risk of inducing contrast nephropathy in human patients with preexisting renal disease could be mitigated by administration of drugs, including mannitol, theophylline, calcium-channel blockers, diuretics, fenoldopam, or dopamine.[37-42] The most recent analyses, however, have failed to identify any pharmacological manipulation superior to simple hydration in reduction of the risk of contrast nephropathy in at-risk populations.[37]

TREATMENT

Medical Management

Initial medical therapy for AUO centers on judicious diuresis (crystalloids, with or without furosemide and/or mannitol) and routine management of the sequelae of uremia (with gastric protectants, antiemetics, antihypertensives, erythropoietic agents/blood products, chlorhexidine oral rinses, and so forth.). If hyperkalemia and volume overload are not present (or if dialytic therapy is available to mitigate these problems), medical management for 3 to 5 days may permit spontaneous resolution of obstruction. Clinical evidence suggests that resolution occurs in approximately 20 per cent of affected cats.[2] Diuresis must be undertaken with foresight, caution, and rigorous monitoring, however. Even in cats producing urine, intractable volume overload can occur rapidly and become life threatening swiftly. Oligoanuric cats that have not responded to medical therapy within 24 hours probably are better served by early surgical intervention (if stable), or by dialytic management followed by surgery if necessary.

Glucagon has been used as an adjunctive therapy for AUO in human beings and cats and decreases ureteral peristalsis markedly and increases renal blood flow.[12,13,43] The single retrospective study done in cats with AUO given glucagon did not demonstrate any improvement in overall outcome with its use, although it was associated with conversion from oligoanuria in several cats[44] and did seem subjectively to be an effective analgesic. In another recent study, Achar, Achar, Paiva, et al[45] treated 20 cats with naturally occurring urethral obstruction with oral amitriptyline (1 mg/kg PO q24h) and achieved 100 per cent passage of the urethral obstruction, presumably because of urethral smooth muscle relaxation. Achar's group proceeded to examine the effect of amitriptyline on smooth muscle in other parts of the urinary tract in human and pig tissue and found that this drug also has potent, lasting, reversible relaxant effects on porcine and human ureteral ring segments.[45] Oral amitriptyline certainly merits investigation as a medical intervention for feline AUO, and further study of glucagons also may be warranted.

Lithotripsy

Extracorporeal shock wave lithotripsy (ESWL) is available at a few veterinary teaching hospitals, and a limited but growing number of clinical cases of feline ureteral obstruction have been managed successfully with this noninvasive modality.[46] Lithotripsy is a potentially valuable means of nonsurgical intervention in this disease process, if it is a geographically feasible referral option. Use of ESWL in cats is discussed in Chapter 44.

Surgical Management

The majority of cats with AUO require surgical management for successful outcome. In a recent retrospective study, 65 per cent of the cats with AUO presented for hemodialysis required surgical correction of the obstruction.[2] The specific surgical intervention selected depends in large part on the location of the obstruction along the length of the ureter. Obstruction occurring in the proximal one third of the ureter generally is managed by ureterotomy or pyeloureterotomy.[5,9] This approach has the advantage of surgical manipulation of an anatomically larger area (i.e., the renal pelvis and dilated proximal ureter), compared with operation on a nondilated ureter and thus should result in decreased risk of postoperative ureteral obstruction from swelling or stricture. Gentle attempts may be made to milk palpable stones lodged in a nondilated or less dilated region of ureter to a proximal area of greater dilation for removal.

Ureteral obstruction occurring in the distal two thirds of the ureter most often is managed with ureteroneocystostomy, particularly when the regional ureter is relatively nondilated.[5,9] Ureteroneocystostomy entails transection of the ureter just proximal to the obstruction, with subsequent reimplantation of the proximal ureter into the bladder apex. The remnant distal ureteral segment is resected. This type of reconstruction carries less risk of postoperative obstruction because of stricture or swelling than does ureteral resection and anastomosis or ureterotomy on the nondilated feline ureter. Extravesicular and intravesicular techniques for ureteroneocystostomy have been well described; in feline patients, particularly those with minimal ureteral dilation, the modified Lich-Gregoir extravesicular technique often is preferred because it results in less postsurgical swelling and consequently a reduced occurrence of postsurgical ureteral obstruction.[47] The intravesical mucosal apposition technique also has been used successfully in cats with AUO in my practice. Both approaches have been detailed in recent reviews.[5,48]

Application of ureteroneocystostomy is limited by the length of ureter available proximal to the obstruction and the consequent tension placed on the surgical repair. Renal descensus and psoas cystopexy are techniques that bring the kidney and bladder into closer apposition and allow ureteroneocystostomy to be performed with more proximal obstructions.[9,49] Renal descensus entails dissection of the kidney from its peritoneal attachments, caudal repositioning, and nephropexy to the body wall. This maneuver fixes the kidney in a more caudal position and prevents torsion about the renal vessels. In psoas cystopexy, the apex of the bladder is pulled craniolaterally toward the affected kidney and then is sutured dorsally to the psoas muscle. An alternate technique, nephrocystopexy, entails dissection of the affected kidney from its peritoneal attachments and suturing of the caudal pole to the bladder apex.[5]

If extensive ureteral damage or stricture is present in the proximal ureter, ureteroureterostomy (ureteral resection and reanastomosis) may be performed, although this technique carries a higher risk of postoperative stricture than ureteroneocystostomy.[5] Alternatively, transureteroureterostomy may be performed. In this technique, partial ureteral amputation is performed proximal to the obstruction and the free ureteral end is anastomosed to the contralateral ureter.[5] Both of these

techniques are recommended only when ureteroneocystostomy is not possible.[5]

Perioperative Management

Significant postoperative complications occur in 30 per cent of surgically managed AUO cats.[13] The most common major postoperative complications are ureteral obstruction and urine leakage into the abdomen. Small defects in the ureteral repair that result in uroabdomen may be medically managed successfully with peritoneal drainage and lavage for 48 to 72 hours, which allows time for healing of the ureteral urothelium. Large defects or severe uroabdomen, however, may require reoperation and surgical revision. Placement of a nephrostomy tube for urine diversion may prove useful before and/or after surgical correction of the obstruction. In emergent, particularly hyperkalemic, cases when dialytic stabilization is not readily available, percutaneous or surgical placement of a nephrostomy tube into the pelvis of the obstructed kidney can facilitate management of azotemia and electrolyte imbalances and permit evaluation of renal function before major surgical intervention.[5,6] Nephrostomy tubes also can be advantageous after ureteral surgery, should ureteral swelling cause transient reobstruction. Complications associated with nephrostomy tubes include tube occlusion, dislodgement from the kidney, and intraabdominal urine leakage. Because of the fragile nature of these cases in the immediate postoperative period, access to dialytic support is of great value in improving outcomes. In one series, 55 per cent of AUO cats managed surgically required temporary postsurgical dialytic management.[2]

In the instance of irreparable surgical failure or severely diseased native kidneys in a cat with AUO, renal allografting remains a viable option for patient salvage.[50,51] Oxalate stone formation is not an absolute contraindication to transplantation; however, owners must be aware of the risk that despite preventive measures, oxalate stones may form in the transplanted kidney and result in recurrence of AUO. Urine cultures (obtained preferably from both the bladder and the obstructed renal pelvis) must be negative. If urinary tract infection is documented, serial negative cultures over several months must be obtained before transplantation, and a challenge with cyclosporine is warranted before the actual transplant procedure.

PROGNOSIS

In severely uremic AUO cats presented for dialytic management, an overall survival rate of 70 per cent has been achieved with aggressive management.[2] Of 50 cats reviewed, survival rates were 61 per cent of those undergoing hemodialysis alone, 60 per cent of those receiving hemodialysis before surgery, and 76 per cent of those managed with hemodialysis both before and after surgery.[2] Of the 35 surviving cats, 71 per cent left the hospital with residual mild to moderate azotemia (non–dialysis-dependent chronic renal failure).[2] In particular, cats with ureteral calculi exhibit an overall surgical survival rate (with and without hemodialysis) of 81 per cent.[13]

PREVENTION OF RECURRENCE

Despite successful surgical or medical management, recurrent ureteral obstruction has been observed in treated cats, in addition to in the grafted kidney of transplanted cats. Recovery and analysis of the obstructing material are critical in devising the optimal management strategy for postobstructed AUO cats. Cats usually require a regimen designed for calcium oxalate stone prevention (see Chapters 43 and 46), but a significant percentage of cats also require management of ongoing mild to moderate chronic renal failure (see Chapter 42). All possible measures should be taken to prevent recurrence of calcium oxalate stone formation to minimize recurrence of AUO.

SUMMARY

The incidence of AUO in cats has increased markedly over the last decade, chiefly because of the increased incidence of calcium oxalate urolithiasis. AUO rapidly becomes life threatening and requires the prompt application of appropriate medical and/or surgical management strategies. Diagnosis relies on a high index of suspicion for AUO and careful radiographic and ultrasonographic evaluation. Prognosis for survival and long-term outcome can be good if microsurgical and dialytic therapies are available, but most cats have some degree of azotemia upon recovery because of preexisting chronic renal failure and additional damage to the obstructed kidney(s). Novel pharmacotherapies and ESWL may play more prominent roles in the management of feline AUO in the future.

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Chapter 42

Clinical Progression of Early Chronic Renal Failure and Implications for Management

Sheri J. Ross, David J. Polzin, and Carl A. Osborne

EPIDEMIOLOGY

Chronic kidney disease (CKD) is a major health problem that affects geriatric cats, and the frequency with which it is diagnosed has increased significantly over the past decade. During 1990, the prevalence of renal failure among cats of all ages was 16 cases for every 1000 cats examined. During the same year, the prevalence of renal failure among cats 10 years of age or older was 77 per 1000 cats examined, and among cats older than 15 years, 153 per 1000.[1]

A recent survey of the Purdue Veterinary Medical Database of all feline cases during the year 2000 indicated the prevalence of CKD has risen dramatically. During the year 2000, the prevalence of CKD among cats of all ages had increased to 112 cases for every 1000 cats examined, whereas prevalence among cats 10 years of age and older was 269 per 1000 cats examined, and among cats over 15 years of age, 491 per 1000. The frequency of which renal failure was identified in female cats was similar to that of male cats (1.06:1), whereas the male-to-female ratio for the entire population of cats was 1.15:1. Compared with the average, however, renal failure was recognized more than five times as often in the following breeds: British shorthair, Birman, Somali, and Angora (Table 42-1).

The marked increase in prevalence of CKD in cats during 2000 as compared with 1990 may be due to increased recognition of the disease through diagnostic screening or a true increase in the incidence of CKD in the feline population.

ETIOLOGY

CKD is the result of damage to a sufficient population of nephrons to impair the normal excretory, regulatory, and endocrine functions of the kidney permanently. A variety of diseases may affect the kidneys and lead to progressive damage and loss of functioning nephrons (Table 42-2). In a study of biopsy findings in 47 cats with primary renal azotemia (serum creatinine concentration >2.0 mg/dl), chronic tubulointerstitial nephritis was observed in 70.4 per cent of samples, glomerulopathy was observed in 14.8 per cent, malignant lymphosarcoma in 10.6 per cent, amyloidosis in 2.1 per cent, and tubulonephrosis in 2.1 per cent.[2] Unfortunately, the histological diagnosis of tubulointerstitial nephritis does not aid in the identification of the underlying etiology and probably represents the final common pathway for progression of many feline renal diseases.

STAGING

Kidney damage is defined as any pathological abnormality or marker of injury, including abnormalities in hematology or serum chemistries, albuminuria, abnormal urine sediment, aberrations noted in imaging studies, and hypertension (Table 42-3). Detection of these indicators of early kidney disease allows for the initiation of measures that could prevent loss of kidney function in some patients and slow progression of the kidney disease in many patients.[3]

Table 42-1 | **Prevalence and Risk of Renal Failure Identified in Cats of Different Breeds**

BREED	PREVALENCE			RISK	
	PER CENT OF BREED	NO.	PER CENT OF TOTAL POPULATION	ODDS RATIO	95 PER CENT CI
British shorthair	100	7 of 7	0.69	N/A	N/A
Birman	68.2	15 of 22	1.29	18.96	7.72-46.61
Somali	41.7	5 of 12	0.43	6.27	1.99-19.78
Angora	36.4	4 of 11	0.34	5.01	1.46-17.14
Unassigned	26.7	35 of 131	3.00	3.25	2.20-4.82
Exotic shorthair	25.0	3 of 12	0.26	2.92	0.79-10.80
Siamese	20.5	84 of 409	7.20	2.36	1.84-3.02
Abyssinian	14.6	7 of 48	0.60	1.49	0.67-3.34
Russian blue	13.3	4 of 30	0.34	1.35	0.47-3.86
Burmese	12.1	4 of 33	0.34	1.21	0.42-3.44
DSH	11.7	688 of 5867	59.01	1.39	1.23-1.57
Tonkinese	11.1	2 of 18	0.17	1.09	0.25-4.76
Maine coon	10.6	15 of 141	1.29	1.04	0.61-1.78
Persian	9.9	21 of 213	1.80	0.96	0.31-1.51
Bengal	9.1	1 of 11	0.09	0.87	0.11-6.83
Mixed (incl. DLH)	8.8	249 of 2824	21.36	0.80	0.69-0.93
Himalayan	8.1	10 of 123	0.86	0.77	0.40-1.48
Norwegian forest cat	7.8	9 of 116	0.77	0.73	0.37-1.45
Rex (Cornish/Devon)	4.8	1 of 21	0.09	0.44	0.06-3.26
Manx	1.8	1 of 55	0.09	0.16	0.02-1.17

Breeds of cats examined in which renal failure was not recorded were American wirehair (2), Balinese (1), Bombay (3), Chartreux (3), Egyptian mau (2), Havana brown (2), Japanese bobtail (2), Maltese (1), Manxamese (1), ocicat (10), Oriental shorthair (15), ragdoll (32), Scottish fold (9), snowshoe (1), and Turkish van (3).
N/A, Unable to calculate; *DLH,* domestic long-haired; *DSH,* domestic short-haired; *CI*, confidence interval.

Table 42-2 | **Some Disorders That May Cause Feline Chronic Kidney Disease**

CONGENITAL

1. Polycystic disease in Persians and Himalayans
2. Amyloidosis in Abyssinian and Oriental shorthair cats

ACQUIRED

1. Sequela of acute renal failure
2. Immune complex glomerulonephropathy
   - Feline leukemia virus (FeLV)
   - Mycoplasma polyarthritis
   - Neoplasia associated
3. Infectious
   - Bacterial
     - Chronic pyelonephritis
     - Leptospirosis
   - Viral
     - Feline infectious peritonitis
     - FeLV
     - Feline immunodeficiency virus
   - Fungal
     - Cryptococcosis
     - Blastomycosis
     - Aspergillosis
4. Neoplastic
   - Lymphosarcoma
   - Renal cell carcinoma
   - Nephroblastoma
   - Others
5. Mechanical
   - Nephrolithiasis
   - Spay granuloma
   - Perinephric pseudocysts
6. Idiopathic

Table 42-3 | **Markers of Kidney Damage***

Blood markers	Elevated blood urea nitrogen concentration
	Elevated serum creatinine concentration
	Hyperphosphatemia
	Hyperkalemia or hypokalemia
	Metabolic acidosis
	Hypoalbuminemia
Urine markers	Impaired urine concentrating ability
	Proteinuria
	Cylindruria
	Renal hematuria
	Inappropriate urine pH
	Inappropriate urine glucose concentration
	Cystinuria
Imaging markers—abnormalities in kidney	Size
	Shape
	Location
	Density
	Number

*Markers must be confirmed to be of renal origin to be evidence of kidney damage.
From Polzin DJ, Osborne CA, Ross SJ: Chronic renal failure. In Ettinger SJ, Feldman EC, editors: Textbook of veterinary internal medicine, ed 6, Philadelphia, 2005, Elsevier.

Table 42-4 | **Stages of Feline Chronic Kidney Disease**

STAGE 1 (NONAZOTEMIC)
Markers of renal disease present
Creatinine <1.6 mg/dl Proteinuria: Classify (P/NP/BP) Hypertension: Classify (Hc/Hnc/NH/BH/HND)
STAGE 2 (MILD RENAL AZOTEMIA)
Markers of renal disease present
Creatinine 1.6-2.8 mg/dl Proteinuria: Classify (P/NP/BP) Hypertension: Classify (Hc/Hnc/NH/BH/HND)
STAGE 3 (MODERATE RENAL AZOTEMIA)
Markers of renal disease present
Creatinine 2.9-5.0 mg/dl Proteinuria: Classify (P/NP/BP) Hypertension: Classify (Hc/Hnc/NH/BH/HND)
STAGE 4 (SEVERE RENAL AZOTEMIA)
Markers of renal disease present
Creatinine >5.0 mg/dl Proteinuria: Classify (P/NP/BP) Hypertension: Classify (Hc/Hnc/NH/BH/HND)

P, Proteinuria; *NP,* nonproteinuria; *BP,* borderline proteinuria; *Hc,* hypertension with complications; *Hnc,* hypertension with no complications; *NH,* nonhypertensive; *BH,* borderline hypertensive; *HND,* hypertension not determined.
From Polzin DJ, Osborne CA, Ross SJ: Chronic renal failure. In Ettinger SJ, Feldman EC, editors: Textbook of veterinary internal medicine, ed 6, Philadelphia, 2005, Elsevier.

The International Renal Interest Society (IRIS) recently has introduced a staging system for the classification and stratification of CKD cats (Table 42-4). The purpose of the staging system is to facilitate the application of clinical practice guidelines for evaluation and management of each stage of CKD.[4] Patients are assigned a specific stage of renal disease based on kidney function as determined by serum creatinine concentration. The patient then is further classified according to their systolic blood pressure and the presence or absence of proteinuria. Both hypertension and proteinuria have been identified as important contributors to progressive renal injury in many species, including cats.[5,6] Although the specific cutoff values used to categorize patients with CKD into these stages are inherently arbitrary, staging is useful for establishing prognosis and managing patients with CKD.

PATHOGENESIS

Establishing a Diagnosis of Irreversible Chronic Kidney Disease

Once markers of renal disease have been identified, the clinician is confronted with the task of determining whether the renal dysfunction is acute or chronic. In the majority of cases, historical laboratory data are not available, and the clinician must rely on physical examination findings, current laboratory data, and imaging studies to determine the chronicity of the renal dysfunction. Differentiation of acute renal failure from acute decompensation of CKD often is difficult (Table 42-5). Although patients with acute renal failure may not regain total renal function, most have the potential to regain adequate renal function to sustain life without the need for aggressive, prolonged therapy. Likewise, if acute decompensation of CKD has been caused by reversible factors, timely correction of these factors may result in return of the renal function to baseline.

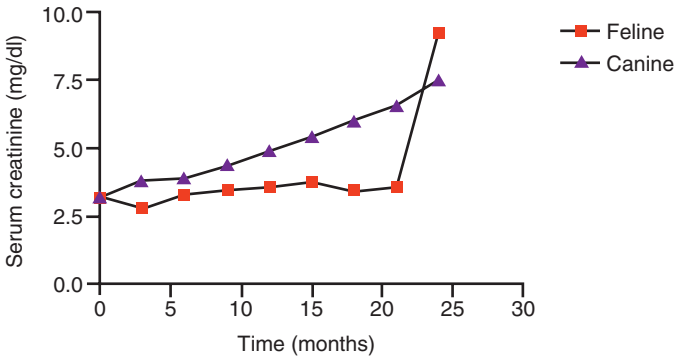

Figure 42-1. Serum creatinine concentrations of a dog and a cat that were monitored serially for 24 months, demonstrating the gradual decline in renal function encountered frequently in dogs and the more abrupt decline observed in many cats.

Whereas acute renal failure is potentially reversible if the underlying cause is identified and corrected quickly, chronic renal failure typically is irreversible and progressive. Historically, progressive kidney disease was thought to occur from continuation or reactivation of the disease that initiated injury to the kidney, or from the superimposition of systemic or metabolic abnormalities onto preexisting kidney disease. Although these two mechanisms still may contribute to the progression of kidney disease, adaptive anatomical and functional changes that occur once the glomerular filtration rate (GFR) falls below a critical level may lead to progressive renal damage, even when the initiating insult has been removed and the kidney is protected from further insults.[7]

Patterns of Progression

Chronic renal failure in human beings, dogs, and rats typically is progressive in nature, which culminates eventually in end-stage kidney disease and death.[7,8] Although cats with CKD may survive for months to years after their initial diagnosis with minimal clinical signs attributable to their renal disease, many cats ultimately develop signs associated with advanced CKD, which indicates that progressive renal injury does occur.[9]

Recent studies have revealed that the pattern of progressive kidney damage observed in cats may be different from that of dogs, rats, and human beings. Although these species seem to have a linear pattern of progression of CKD, progression in many cats seems to manifest as abrupt increases in serum creatinine concentration after variable periods of clinical quiescence. A longitudinal study of the impact of metabolic acidosis on the progression of naturally occurring renal disease in 55 cats revealed that 60 per cent of the cats did not show evidence of progression, whereas 25 per cent showed stepwise progression and 15 per cent demonstrated linear progression.[10] A recent clinical trial of 45 cats with spontaneous CKD demonstrated stable renal function in 40 cats for up to 24 months. The five cats that developed uremic crises during the study demonstrated an abrupt increase (43 to 371 per cent) in serum creatinine concentration after 3 to 21 months of stable renal function.[11] Figure 42-1 demonstrates the patterns of progressive deterioration in renal function observed in a cat and a dog that were monitored serially for 24 months.

Table 42-5 | **Typical Similarities and Differences Between Patients with Acute Renal Failure, Chronic Renal Failure, and Acute Decompensation of Chronic Renal Failure**

	CHRONIC	ACUTE	ACUTE ON CHRONIC
HISTORY AND PHYSICAL EXAM			
Recent exposure to nephrotoxin or ischemic episode	Unlikely	Probable	Possible
Weight loss	Chronic because of tissue loss	Acute because of fluid loss	Tissue and fluid loss
Urine volume	Prolonged polyuria	Variable	Oliguria preceded by prolonged polyuria
Relative severity of signs for comparable degree of azotemia	Mild; compensatory adaptations	Marked	Moderate
Renal size and shape	Often decreased; may be normal or unequal in size	Normal to increased	Decreased, may be normal or increased
Renal surface contour	Often irregular	Smooth	Often irregular
BLOOD CHEMISTRY			
Serum urea nitrogen	Increased	Increased	Increased
Serum creatinine	Increased	Increased	Increased
Serum phosphorus	Increased	Increased	Increased
Serum calcium	Usually normal to decreased; may be increased	Variable, dependent on cause	Usually normal to decreased; may be increased
Serum potassium	Normal if polyuric; increased if oliguric	Increased if oliguric; normal if polyuric	Normal if polyuric; increased if oliguric
Blood bicarbonate (metabolic acidosis)	Mild to moderate decrease	Moderate to severe decrease	Moderate to severe decrease
HEMOGRAM			
PCV and hemoglobin	Normal to decreased (nonregenerative)	Variable	Normal to decreased (nonregenerative)
URINALYSIS			
Concentrating/diluting ability	Isosthenuric	Isosthenuric	Isosthenuric
Glucosuria	Uncommon	Variable	Uncommon
Pyuria	Variable	Variable	Variable
Crystalluria	Uncommon	Possible; dependent upon etiology	Uncommon
Proteinuria	Variable	Variable	Variable
Tubular casts	Uncommon	Variable; dependent upon etiology	Possible

This pattern of stepwise progression in cats has important clinical implications for the management of early CKD, because therapeutic interventions often are initiated only after evidence of progression has occurred. Dietary modifications such as protein and phosphorus restriction have been the cornerstone of medical management of feline CKD. Traditionally, the timing for dietary and medical intervention for cats with early CKD has been based on empirical observations. Little debate exists regarding whether cats with advanced CKD and clinical signs associated with uremia benefit from dietary modifications. However, recent clinical studies indicate that initiating dietary therapy in cats with less advanced stages of CKD may be beneficial.

Importance of Early Intervention

Beneficial effects of dietary modifications were observed in a nonrandomized, open clinical trial of 50 cats with naturally occurring CKD.[12] Renal-related mortality in 29 cats fed a diet restricted in protein and phosphorus was approximately 33 per cent, compared with 52 per cent mortality in 21 cats fed an unrestricted diet. Overall, this dietary clinical trial identified a median survival time of 264 days for cats without dietary intervention and a median survival time of 633 days for cats fed a modified renal failure diet. A 24-month, randomized, double-masked, controlled clinical trial evaluating the effects of dietary modifications on 45 cats with spontaneous CKD was completed recently at the University of Minnesota. Renal-related mortality in 23 cats fed an adult maintenance diet was 17.4 per cent, although no deaths were observed in 22 cats fed a diet restricted in protein and phosphorus.[11] The results of these clinical trials support the use of dietary modification early in the management of cats with spontaneous CKD.

Ideally, the clinician would be able to identify which cats are most likely to progress and intervene before the development of a uremic crisis. Unfortunately, retrospective analysis of the biochemical and clinical data from the clinical trial at the University of Minnesota did not identify any markers that could be used to predict which cats would develop uremic crises and which cats would remain clinically stable.[11] Until such markers are identified, we recommend that dietary intervention be initiated before the onset of clinical signs of uremia or detectable progression of renal disease.

Clinical Signs and Diagnosis

Early detection of CKD in cats and dogs currently is an active area of research in veterinary medicine. Many cats in the early stages of kidney disease may be asymptomatic, or they may develop subtle, nonlocalizing clinical signs often mistaken as

Table 42-6 | **Historical and Physical Examination Findings Often Associated with Chronic Kidney Disease**

HISTORICAL FINDINGS	PHYSICAL EXAMINATION FINDINGS
Weight loss	Poor body condition
Anorexia/inappetence	Poor haircoat
Depression	Dehydration
Polydipsia	Periodontal disease
Polyuria	Heart murmur
Vomiting	Small kidney(s)
Weakness	Pallor
Constipation	Palpable thyroid gland

Table 42-7 | **Problem Specific Database for Patients with Chronic Kidney Disease**

- Medical history
  - Include historical laboratory values
  - Review current and past medications
- Physical examination including retinal fundus
- Urinalysis
- Urine microalbuminuria screen
- Urine culture
- Complete blood count
- Urine protein:creatinine ratio (if indicated by urinalysis/microalbuminuria screen)
- Serum urea nitrogen concentration
- Serum creatinine concentration
- Serum (or plasma) electrolyte and acid-base profile, including the following:
  - Sodium, potassium, and chloride concentrations
  - Blood gas analysis or total serum CO_2 concentrations
  - Calcium, phosphorus, and albumin concentrations
- Arterial blood pressure
- Kidney-bladder-urethra survey radiographs
  - Kidneys: size, shape, location, number
  - Uroliths or masses affecting kidneys, ureters, or urethra
  - Urinary bladder: size, shape, location, uroliths
- Consider:
  - Additional imaging studies as indicated (rule out urinary obstruction, nephroliths, pyelonephritis, cystic renal disease, perinephric pseudocysts, and renal neoplasia):
    - Renal ultrasound
    - Intravenous urography
    - Pyelogram
  - Determining glomerular filtration rate
    - Plasma clearance of iohexol, inulin, creatinine, or other
  - Determining serum parathyroid hormone and ionized calcium concentrations for managing renal secondary hyperparathyroidism
  - Renal biopsy
- Before initiation of therapy, freezing aliquots of serum (or plasma) and urine for additional diagnostics that may be desired later

age-related changes by the owners. Some of the most common clinical signs observed in cats with CKD are listed in Table 42-6. Given the paucity of clinical signs associated with early CKD, and that the estimated incidence of CKD is 30 per cent for cats greater than 10 years of age and 50 per cent for those greater than 15 years of age, routine laboratory screening of geriatric cats for evidence of CKD is critical. We recommend that cats older than 10 years of age undergo yearly evaluation for markers of kidney damage. This evaluation minimally should include determination of serum creatinine concentration, measurement of urine specific gravity, and qualitative assessment of urine protein concentration. We also recommend that abdominal radiographs be performed at 10 years of age and repeated as necessary to detect and monitor nephroliths.

The diagnosis of chronic renal failure usually is confirmed by demonstration of inadequate urine concentrating ability (urine specific gravity less than 1.035) in an azotemic patient. Although other conditions may cause impaired urine concentrating ability associated with prerenal azotemia, they are uncommon and usually are apparent when the patient's history and other laboratory findings are examined. When a diagnosis of CKD is suspected based on results of initial screening, the patient should be evaluated further to stage the CKD and to identify complications or concurrent diseases that could adversely affect progression or therapy. Diagnostic recommendations for further evaluation of cats with CKD are outlined in Table 42-7.

Serum creatinine concentration has been the measure of renal function used most commonly and usually is the basis for staging CKD. However, factors other than GFR, such as lean body mass, affect serum creatinine concentration. Therefore these determinations may not always be accurate estimates of renal function, especially in patients with mild renal insufficiency. To optimize accuracy of staging of CKD, serum creatinine concentrations used to stage CKD should be evaluated when the patient is well hydrated. Multiple measurements are desirable to establish accuracy and stability of renal dysfunction. Serum creatinine concentrations associated with progressive muscle wasting must be interpreted with caution, because endogenous production of creatinine from muscle creatine may decline and thereby confound interpretation of serial serum creatinine values.[13]

Ideally, the severity of a patient's CKD would be measured using GFR, which generally is considered the best overall index of renal function. GFR may be determined by measurement of plasma clearances of iohexol, inulin, or other substances excreted exclusively by the kidneys. However, technical and economic constraints have limited the routine use of these procedures. Most clinicians continue to use serum creatinine concentration for diagnosis and monitoring of renal disease.

FACTORS INFLUENCING PROGRESSION OF CHRONIC KIDNEY DISEASE

Dietary Modification

In experimental renal disease in rats, dietary protein restriction decreases intraglomerular pressure and retards the decline of renal function. Clinical trials of protein restriction in human beings, however, have yielded variable results. Some studies have shown no benefit with regard to the rate of loss of renal function, whereas others have found that progression of renal disease is ameliorated by a low-protein diet.

Three studies have evaluated the effects of restriction of dietary protein and/or phosphorus in cats with induced kidney disease.[14-16] Although Ross, Finco, and Crowell[14] found significantly more renal morphological changes and greater serum phosphorus levels in cats with 5/6 nephrectomy fed a high-phosphorus diet compared with a low-phosphorus diet, a corresponding decrease in GFR was not correlated with these changes. In cats with 5/6 nephrectomy, Adams, Polzin, Osborne, et al[15] found that restricting dietary protein (to approximately 2.7 g/kg/day) and energy intake (to approximately

56 kcal/day) resulted in a significant decrease in morphological lesions, compared with consumption of approximately 6.8 g protein/kg/day and 75 kcal/day. The GFR of the cats in this study was not significantly different between groups nor within groups. The study by Finco, Brown, Brown, et al[16] did not demonstrate morphological differences or changes in GFR between cats with 11/12 nephrectomy consuming different dietary protein levels (approximately 5.3 or 9.0 g/kg/day), and only minor differences in morphology when different caloric intakes were examined. Although evidence of morphological changes was observed in some cats in these studies, the GFRs in all groups remained stable over the 12-month period of study.

Beneficial effects of dietary modifications were observed in a nonrandomized, open clinical trial of 50 cats with naturally occurring CKD.[12] Renal-related mortality in 29 cats fed a diet restricted in protein and phosphorus was approximately 33 per cent compared with 52 per cent mortality in 21 cats fed an unrestricted diet. Overall, this dietary clinical trial identified a median survival time of 264 days for cats without dietary intervention, and a median survival time of 633 days for cats fed a diet modified for renal failure. A 24-month, randomized, double-masked, controlled clinical trial that evaluated the effects of dietary modifications on 45 cats with spontaneous CKD was completed recently at the University of Minnesota. Renal-related mortality in 23 cats fed an adult maintenance diet was 17.4 per cent, although no deaths were observed in 22 cats fed a diet restricted in protein and phosphorus.

The results of these clinical trials support the early intervention with dietary modification in cats with spontaneous CKD. The question of timing of dietary intervention also is important. Traditionally, dietary intervention has been recommended based on hematological or biochemical values, or biochemical evidence of progression of the renal disease. Early dietary intervention may be particularly beneficial in cats with a long period of clinical quiescence during which minimal detectable progression is followed by abrupt deterioration in renal function. Given this pattern of disease progression, early dietary intervention before the onset of signs of uremia may minimize progression of renal disease.

Hyperphosphatemia

Elevated serum phosphorus concentrations are common in CKD and play a critical role in the pathogenesis of renal secondary hyperparathyroidism. A recent clinical trial demonstrated that control of serum phosphorus concentration, using dietary modification and oral phosphate binders, increased survival times in cats with CKD.[17] Hyperphosphatemia inhibits the conversion of 25-hydroxyvitamin D to the active metabolite 1,25-dihydroxyvitamin D3 (calcitriol). The decreased levels of calcitriol lead to a decreased circulating ionized calcium concentration, which stimulates the production of parathyroid hormone (PTH).[18]

Dietary phosphorus restriction is indicated in all patients with an elevated serum phosphorus concentration. Dietary phosphorus restriction may be implemented in the early stages of CKD, because phosphorus retention and hyperparathyroidism likely are present even when the serum phosphorus concentration is within the normal range.[19] The majority of commercial diets formulated for the treatment of renal disease in cats have a restricted phosphorus content (<0.6 per cent dry matter basis).

If hyperphosphatemia persists despite dietary phosphorus restriction, oral phosphate binding agents should be considered. The most commonly used phosphorus-binding agents are aluminum-based or calcium-based compounds that bind intestinal phosphorus in exchange for their cation. The phosphorus-binding agent should be administered at the time of feeding so that they may minimize absorption of ingested phosphorus.

Aluminum-based compounds (aluminum hydroxide, aluminum carbonate) are inexpensive, efficient phosphorus binders with minimal side effects in cats; however, declining use in human medicine because of neurological and bone toxicity with extended use is making them more difficult to find. Readily available calcium-based phosphorus-binding agents include calcium acetate, calcium carbonate, or calcium citrate. Calcium-based drugs have the potential to promote significant hypercalcemia in cats, particularly when administered between meals or used in combination with calcitriol.

Dosages vary among patients and should be adjusted according to the target serum phosphorus concentration. The goal of dietary restriction and use of phosphate-binding agents is to keep serum phosphorus within the normal laboratory range. Recent studies in human beings indicate that maintaining serum phosphorus concentration at the lower end of the reference range was superior to reducing serum phosphorus concentration to the high end of the reference range.[20] Furthermore, to prevent soft tissue deposition of calcium-phosphate complexes, the product of calcium and phosphorus must be kept below 70.

Recently, polyallylamine hydrochloride (RenaGel, Geltex Pharmaceuticals, Waltham, MA), an aluminum-free and calcium-free phosphate-binding polymer, has been shown to bind dietary phosphorus effectively in human patients with chronic renal failure on maintenance hemodialysis. This polymer was comparable to calcium carbonate and calcium acetate in binding phosphorus without any changes in serum calcium concentrations.[21,22] Preclinical studies in rats and dogs using several times the recommended dose resulted in reduced vitamin D, E, K, and folic acid levels. Safety and efficacy information was not available for its use in cats. Polyallylamine hydrochloride may prove to be a safe and effective alternative to calcium salts for the management of hyperphosphatemia in cats with CKD; however, controlled clinical trials are needed to prove its efficacy.

Hypertension

Systemic hypertension has been recognized commonly in association with many diseases and has been implicated as a major determinant in the progression of CKD in human beings and dogs.[23,24] A recent study of the prevalence of systolic hypertension in cats with CKD indicated that 20 per cent of cats with CKD were hypertensive at initial evaluation.[5] The general consensus among veterinary nephrologists is that systolic blood pressures exceeding 160 mm Hg may lead to end-organ injury and progression of underlying kidney damage. Hypertension therefore warrants detection and treatment.[13]

Hypertension usually is a consequence rather than a cause of CKD in dogs and cats. Although microscopic renal lesions suggestive of hypertensive injury have been identified in the kidneys of dogs and cats, they do not develop the syndrome of hypertensive nephropathy encountered commonly in human patients. However, occasionally patients are presented with profound hypertension (>220 mm Hg) in combination with

rapidly deteriorating renal function. Although the hypertension may not be the underlying cause of the renal disease, it may contribute to a rapid decline in renal function and thus aggressive therapy is warranted.

Diagnosis of systemic hypertension should be based on arterial blood pressure determination using either direct or indirect methods. In the absence of end-organ damage, systolic blood pressures less than 200 mm Hg generally do not require immediate therapy and should be confirmed on two to three successive clinic visits to ensure that the observed elevations in blood pressure are not the result of the transient "white coat" effect.[25] Cats with systolic blood pressures repeatedly greater than 160 mm Hg should be treated to minimize the development of end-organ damage (e.g., retinal lesions) and progression of renal disease.[26]

Because of its effectiveness, lack of side effects, and once-daily oral administration, the calcium-channel blocker amlodipine currently is the antihypertensive drug of choice in cats.[27,28] Amlodipine initially is prescribed at a dose of 0.625 mg/cat and may be increased to 1.25 mg/cat in larger patients or if the desired effect is not obtained at the lower dosage. If the blood pressure cannot be controlled with amlodipine, the addition of an angiotensin-converting enzyme (ACE) inhibitor should be considered.[29,30] For more information on the use of ACE inhibitors in renal disease, please consult Chapter 45 of this text.

Proteinuria

In human beings, proteinuria has been identified as an independent risk factor for the progression of chronic renal failure. The magnitude of proteinuria is related inversely to median survival times. Proteinuria also appears to be a risk factor for progression of chronic renal disease in cats and may be associated therefore with decreased survival times.[6,31] Therapy for proteinuria in human beings traditionally has involved ACE inhibitors, which have been shown to reduce the magnitude of proteinuria and increase survival times.

A recent 3-year clinical trial demonstrated that treatment with an ACE inhibitor did reduce the quantity of protein significantly in the urine of cats with spontaneous CRF.[32] However, this reduction in protein was not associated with a significant increase in median survival times. In another study, urine protein:creatinine ratios were useful as a predictor of survival time in cats with spontaneous CRF. In this study, median survival times for cats with UPC less than 0.43 was 766 days, whereas median survival time for cats with UPC greater than 0.43 was only 281 days.[6,31] For more information on the use of ACE inhibitors in feline kidney disease, see Chapter 45.

MANAGEMENT OF SYSTEMIC COMPLICATIONS ASSOCIATED WITH CHRONIC KIDNEY DISEASE

Patients with CKD may experience a myriad of clinical signs as a result of the reduced ability of the kidneys to perform three basic functions: regulation of water and electrolytes, excretion of organic solutes, and the production of hormones. The goal of medical management of CKD is to minimize clinical signs and progression of disease by correcting deficits and excesses in fluid, electrolyte, acid-base, and hormones, and to minimize retention of metabolic wastes. Although the onset of polysystemic clinical signs attributable to renal failure typically is slow and insidious, signs of multisystem failure may become evident as renal function declines. However, with early recognition and intervention, many of the complications of CKD can be ameliorated or prevented. Common complications associated with CKD are outlined in Table 42-8 and commonly recommended treatments are listed in Table 42-9.

Table 42-8 | **Some Complications Associated with CKD**

Nonspecific	Gastrointestinal
Dehydration	Anorexia
Uremia	Nausea
Cardiovascular	Vomiting
Hypertension	Uremic stomatitis
Electrolyte and acid-base balance	Malnutrition
Metabolic acidosis	Urinary
Hypo-/hyperkalemia	Polyuria/polydipsia
Hypo-/hypercalcemia	Proteinuria
Hyperphosphatemia	Neurological/musculoskeletal
Hematological/endocrine abnormalities	Encephalopathy
Renal secondary hyperparathyroidism	Peripheral neuropathy
Hypoproliferative anemia	Myopathy
Platelet dysfunction	Renal osteodystrophy

Metabolic Acidosis

Metabolic acidosis is a common complication of the later stages of CKD. In a retrospective case series of cats with renal failure, almost 80 per cent had metabolic acidosis as determined by venous blood pH and bicarbonate concentrations.[1] The prevalence of metabolic acidosis in a recent cross-sectional study of 59 cats with naturally occurring CKD was 52.6 per cent in cats with stage 4 CKD, 15 per cent in those with stage 3 CKD, and 0 per cent in those with stages 1 and 2 CKD.[10]

As CKD progresses, metabolic acidosis develops as a result of impaired renal tubular ammonia production, decreased urinary excretion of hydrogen ion, and reduced renal tubular reabsorption of bicarbonate. Clinical consequences associated with metabolic acidosis include anorexia, nausea, vomiting, lethargy, muscle wasting, and protein malnutrition. One study of chronic metabolic acidosis in cats demonstrated a negative calcium balance and bone demineralization,[33] whereas another indicated that chronic metabolic acidosis may promote negative potassium balance.[34]

Therapy for metabolic acidosis should be considered when the blood bicarbonate concentration remains below 17 mEq/L on consecutive determinations. Given the questionable accuracy of serum total CO_2 concentrations, we recommend blood gas analysis to confirm metabolic acidosis whenever total CO_2 declines below 15 mmol/L.[35]

Treatment options for metabolic acidosis include use of nonacidifying diets, sodium bicarbonate, and potassium citrate. Most diets formulated specifically for animals with renal failure are designed to be neutral to slightly alkalinizing. Often diet alone may control early acidosis. However, if the acidosis persists or worsens, oral alkalinization with sodium bicarbonate or potassium citrate should be considered. A suggested initial dose of sodium bicarbonate is 8 to 12 mg/kg body weight given every 8 to 12 hours. Often specially compounded formulations are used, because cats find oral sodium bicarbonate unpalatable

Table 42-9 | **Therapeutic Options for the Management of Renal Failure**

TREATABLE ABNORMALITY	THERAPEUTIC OPTIONS
Negative fluid balance	Unlimited access to water If vomiting or unwilling to drink, consider parenteral fluid administration Replace deficit in 6 to 12 hours if animal's condition allows
Metabolic acidosis	Dietary protein reduction Avoid diets producing acidic urine Sodium bicarbonate (10 mg/kg q8-12h) Potassium citrate (40-60 mg/kg q12h) (Caution: may enhance intestinal absorption of aluminum, resulting in toxicity)
Hyperphosphatemia	Correct dehydration Dietary protein reduction Intestinal phosphate-binding agents Aluminum hydroxide (30-90 mg/kg/day PO) Calcium carbonate (100 mg/kg/day PO) Others
Hypoproliferative anemia	Minimize blood sampling Erythropoietin replacement Consider if Hct below +/– 18 per cent Epogen (50-100 U/kg three times a week) increase dose interval when Hct > +/– 35 per cent Always provide supplemental iron when using exogenous erythropoietin
Systemic hypertension	Gradual dietary sodium reduction Amlodipine (0.625 mg/cat q24h) Enalapril (0.25 mg/kg q12-24h) Others/combinations
Hypokalemia	Oral potassium supplementation Potassium gluconate (2-4 mEq q8-12h) Potassium citrate (40-60 mg/kg q12h) Parenteral potassium supplementation
Hypocalcemia	Verify absolute hypocalcemia First correct hyperphosphatemia Oral calcium supplementation Vitamin D therapy (calcitriol 1.5-3.5 ng/kg/day PO)
Hypercalcemia	Correction dehydration Correct hyperphosphatemia Others
Renal secondary hyperparathyroidism	Correct hyperphosphatemia Vitamin D therapy (calcitriol 1.5-3.5 ng/kg/day PO)

and commercially available tablets usually are large, which makes administration difficult. Alternatively, potassium citrate may be used at a starting dose of 40 to 60 mg/kg PO q8-12h. Potassium citrate also allows for the simultaneous treatment of acidosis and hypokalemia in cats requiring therapy for both disorders.

Response to therapy should be assessed after 10 to 14 days by evaluation of blood bicarbonate concentrations. Ideally, the sample should be collected just before administration of the drug. The dosage of medication should be adjusted to maintain the blood bicarbonate concentration within the normal range.

Electrolyte Abnormalities

Hypokalemia (serum potassium concentration less than 3.5 mEq/L) is a relatively common laboratory finding in cats with CKD, with prevalence estimates ranging from 20 to 30 per cent.[1,9,36] Factors implicated in the development of hypokalemia include inadequate dietary intake resulting from inappetence or low potassium content of the diet, metabolic acidosis, and increased urinary and fecal loss. Hypokalemia has been associated with many clinical signs including anorexia, vomiting, weight loss, lethargy, generalized muscle weakness, cardiac arrhythmias, and progression of renal failure.[37]

Oral administration is the preferred and safest route for potassium supplementation. Potassium chloride generally is not recommended for oral supplementation because it is unpalatable and acidifying and may cause gastrointestinal upset. Potassium may be supplemented orally as gluconate or citrate salts. Potassium gluconate is available for oral administration as tablets, flavored gel, or in a flavored powder form (Tumil-K, Virbac Corp., Fort Worth, TX). Starting doses vary with the degree of hypokalemia and the size of the cat but typically are 2 to 6 mEq per cat per day. Alternatively, potassium citrate oral solution may be given at a dose of 40 to 60 mg/kg/day divided into two or three doses. Potassium citrate is particularly useful if acidosis is coexisting with the hypokalemia. Serum potassium should be monitored within 1 to 2 weeks of initiating therapy, and the dosage should be adjusted to maintain a serum potassium concentration greater than 4.0 mEq/L.

Renal Secondary Hyperparathyroidism

Renal secondary hyperparathyroidism is an important complication of CKD and may occur early in the course of the disease. It results presumably from the combined influence of phosphorus retention and decreased production of 1,25-dihydroxyvitamin D (calcitriol). In a recent study of cats with spontaneous CRF, the overall prevalence of renal secondary hyperparathyroidism was 84 per cent.[17] Hyperparathyroidism was documented in 100 per cent of cats with end-stage CKD and 47 per cent of clinically normal cats with only biochemi-

cal evidence of CKD. Hyperparathyroidism was detected even in some cats with normal serum calcium and phosphorus concentrations.

Calcitriol (1,25-dihydroxycholecalciferol) is the most biologically active form of vitamin D and is produced by 1-alpha hydroxylation of 25-hydroxycholecalciferol in the kidneys. As functioning renal mass declines, the ability of the kidneys to produce 1-alpha-hydroxylase is impaired, which results in decreased calcitriol concentrations. This leads to a decrease in calcium and phosphorus absorption and ultimately elevated serum parathyroid hormone (PTH) concentrations. PTH is a uremic toxin; elevated serum concentrations have been associated with a variety of physiological abnormalities.

Exogenous administration of calcitriol to dogs and cats has been shown to decrease serum PTH concentrations.[38] Current evidence supporting the use of calcitriol in cats with CKD is limited to a survey of veterinarians who use the drug routinely in the management of their CKD patients. Results of this survey were favorable and imply that patients treated with calcitriol seemed brighter, were more active, had better appetites, and lived longer than cats not treated with the drug. Randomized, controlled clinical trials examining the use of calcitriol in the management of feline CKD currently are in progress.

Before initiation of therapy with calcitriol, the serum phosphorus concentration should be stabilized within the normal range (<6.0 mg/dl). Controlling hyperphosphatemia increases the effectiveness of calcitriol therapy and minimizes the potential for dystrophic mineralization should hypercalcemia occur after therapy has been initiated. Although hypercalcemia apparently does not occur as commonly in veterinary patients as it does in human beings, it is a serious complication that could lead to further renal impairment.[39] Calcium-containing phosphorus binding agents (such as calcium carbonate) must be avoided when using calcitriol, because this combination could potentiate the development of hypercalcemia.

Nagode, Chew, and Podell[38] recommend that calcitriol be given at a dose of 2.5 to 3.5 ng/kg body weight PO per day to cats with CKD. Individual dosage adjustments must be based on serial evaluations of serum calcium, phosphorus, and PTH concentrations. The goal of calcitriol therapy is to normalize the serum PTH concentration without inducing hypercalcemia. After treatment is initiated, the patient's calcium, phosphorus, PTH, creatinine, and serum urea nitrogen levels should be monitored serially (1 week, 1 month, and then every 1 to 2 months).

Anemia

Many cats with stage 3 or 4 CKD develop a normocytic, normochromic, hypoproliferative anemia. Although decreased erythropoietin production is the principal factor responsible for the anemia, other contributing factors may include chronic blood loss, hemolysis, and iron or folic acid deficiencies. Chronic low-grade gastrointestinal blood loss may exacerbate iron deficiency. In a recent study, the serum iron concentrations of three of seven CRF cats were below the reference range.[40]

Recombinant human erythropoietin (rHuEPO) may be beneficial in the treatment of severe anemia associated with CKD. Replacement therapy with rHuEPO should be considered when the patient's hematocrit falls below 20 per cent and clinical signs attributable to anemia are present. Administration of rHuEPO causes a dose-dependent increase in hematocrit.[40] Generally, the hematocrit increases to within the normal range within 3 to 8 weeks. The typical starting dose of rHuEPO for cats is 100 U/kg SQ, three times weekly. The hematocrit should be monitored weekly until the target hematocrit (30 to 40 per cent) is attained, at which point the dosing should be decreased to twice weekly. Further adjustments in the dose or dosing interval should be based on serial evaluations of hematocrit at appropriate intervals.

A supplemental source of iron should be given concurrently with rHuEPO to support the production of new red blood cells. Although oral supplementation with ferrous sulfate or ferrous gluconate is the treatment of choice for iron deficiency anemia, gastrointestinal side effects may limit its use in some patients. Often these side effects can be minimized if the iron is given in small divided doses with food. If the patient cannot tolerate oral iron supplementation, iron dextran may be administered by intramuscular injection. However, occasional anaphylaxis and iron toxicity have been observed with parenteral administration of iron.

Adverse effects related to the administration of rHuEPO in cats may include hypertension, seizures, and development of antierythropoietin antibodies.[40] The administration of rHuEPO may cause hemodynamic alterations that induce or exacerbate hypertension in some cats. Although seizures have been reported in some cats receiving rHuEPO, the underlying mechanism(s) has yet to be elucidated.

The development of refractory anemia and bone marrow hypoplasia secondary to anti-rHuEPO antibodies is a devastating complication of this therapy. Although not all treated individuals develop antibodies, some of those that do have antibodies against endogenous erythropoietin in addition to rHuEPO. Although antibody titers may decline after therapy with rHuEPO is discontinued, many cats become blood transfusion–dependent. Hopefully, the recent development of feline recombinant erythropoietin will improve treatment outcomes for cats with anemia and CKD.[41]

MONITORING CATS WITH CHRONIC KIDNEY DISEASE

Monitoring schedules for cats with CKD should be individualized to the specific need of the patient. Cats in the early stages (1 and 2) of CKD without systemic complications may need to be evaluated only every 4 to 6 months, whereas cats with advanced disease and many systemic complications may require much more intense monitoring. We recommend the initial database be repeated at appropriate intervals based on the stability and clinical condition of the patient. Cats in stages 3 and 4 CKD should be reevaluated about every 2 to 4 months, depending on the stability of their renal function.

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Chapter 43

Upper Tract Uroliths: Questions, Answers, Questions

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Over the past 2 decades, analysis of more than 56,000 feline uroliths at the Minnesota Urolith Center has revealed a significant change in the prevalence of their mineral composition. Although uroliths composed of sterile struvite predominated in the 1980s, the occurrence of calcium oxalate (CaOx) uroliths increased dramatically in the 1990s. Since 1981, the frequency of CaOx has increased more than fiftyfold.

The increase in occurrence of CaOx uroliths in cats has been associated with a parallel increase in occurrence of CaOx uroliths found in their kidneys and ureters. In fact, the frequency of upper tract uroliths diagnosed in cats evaluated at veterinary teaching hospitals in North America has increased tenfold during the past 20 years.[1] CaOx currently is the predominant mineral type in upper tract uroliths submitted to the Minnesota Urolith Center.

The occurrence of upper tract uroliths composed of CaOx poses unique management problems in part because a method to promote medical dissolution of CaOx uroliths has not yet been developed. The problems are magnified in cats with chronic renal failure, because partial or total obstruction of just one ureter with a urolith may precipitate an acute onset of a uremic crisis (so-called "acute-on-chronic" renal failure) (see Chapter 41). Although surgical removal of upper tract uroliths theoretically may decrease the magnitude of renal dysfunction, ureteral surgery has been associated with significant risks, especially irreparable iatrogenic damage to the ureters and kidneys. For these reasons, we have had the best results in managing cats with renal failure and ureteroliths by noninvasive medical protocols. As illustrated in the following case report, we usually avoid surgery unless the patient does not respond to medical therapy, to the extent that the likely benefit of ureteral surgery outweighs the risks. Use of noninvasive procedures (e.g., shock wave lithotripsy and endoscopic laser lithotripsy) to treat human patients with ureteroliths resulted in a significant reduction in iatrogenic loss of renal function associated with surgical intervention[2] (see Chapter 44).

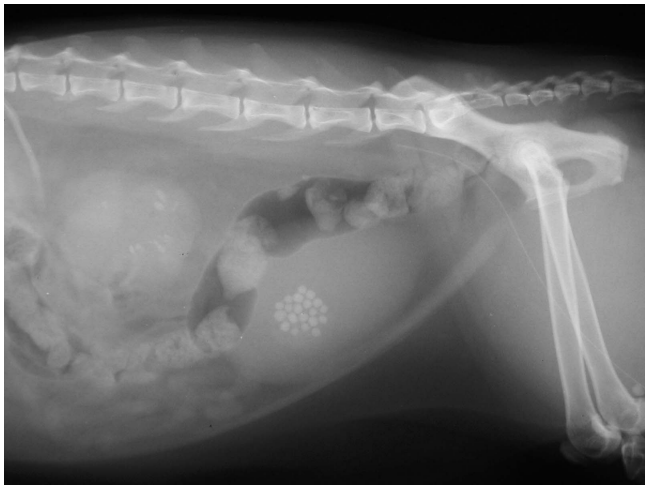
CASE REPORT: DAY 1

An 8-year-old female spayed domestic shorthair cat was evaluated at the University of Minnesota Veterinary Teaching Hospital because of a 2-day history of lethargy, anorexia, and vomiting. The cat had been fed an adult maintenance dry diet. According to the owners, the cat consumed plenty of water. They were unsure about urine volume; however, no evidence of pollakiuria or dysuria was present.

Physical examination revealed that the cat was mildly dehydrated (estimated to be 5 per cent loss of body weight). Temperature (38.3ºC), respirations, pulse rate, and systolic blood pressure were normal. The right kidney was smaller than the left kidney; the urinary bladder was normal.

Results of a serum chemistry profile revealed that the concentrations of creatinine (8.5 mg/dl) and urea nitrogen (117 mg/dl) were increased abnormally. Serum concentrations of phosphorus (6.8 mg/dl), calcium (10.6 mg/dl), and total carbon dioxide (16.3 mmol/L) were normal. Results of a hemogram revealed values within the normal reference range (hematocrit = 41 per cent and white blood cell count [WBC] = 7900/µl). Analysis of a urine sample collected by cystocentesis before any form of therapy revealed it was inappropriately dilute (SG = 1.008) in context of the clinical dehydration and azotemia. The urine was acidic (pH 6.5) and contained evidence of hematuria (RBC > 50/high power field). White cells, bacteria, and crystals were not detected in urine sediment. Aerobic culture of an aliquot of urine collected by cystocentesis did not result in growth of bacteria.

Survey radiographs of the urinary tract revealed bilateral radiodense nephroliths, ureteroliths, and urocystoliths (Figure



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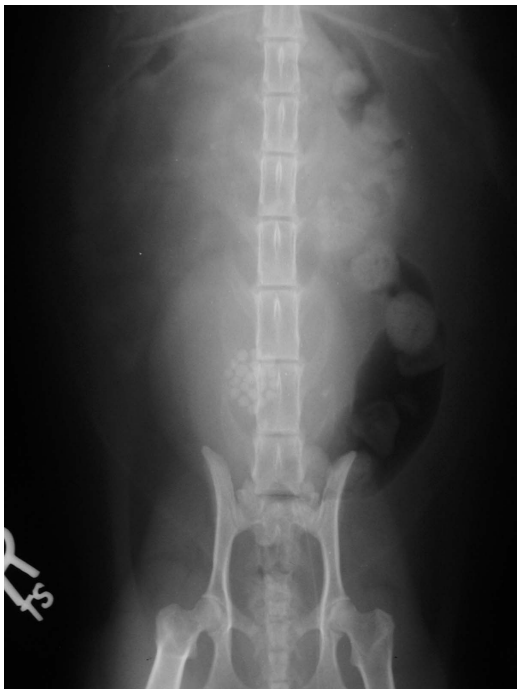

B

Figure 43-1. Survey **(A)** lateral and **(B)** ventrodorsal radiographs of an 8-year-old female spayed, domestic shorthair cat with a 2-day history of anorexia and lethargy. The right kidney is small, measuring 1.0 times the length of the second lumbar vertebra (L2) as measured in the ventral-dorsal projection; the left kidney is of normal length (2.65′ × L2) and both kidneys had an irregular contour. Multiple circular and oval radiopaque structures approximately 1 to 3 mm in diameter are observed in both kidneys, in the retroperitoneal space, and in the urinary bladder consistent with nephroliths, ureteroliths, and urocystoliths. The patient's serum creatinine concentration was elevated (8.4 mg/dL).

43-1). Ultrasonography revealed evidence of urinary outflow obstruction in the proximal portion of the left kidney associated with dilation of the ureter and renal pelvis; however, the resistive index was normal. A diagnosis of chronic azotemic polyuric renal failure associated with nephroliths, ureteroliths, and urocystoliths was made. The azotemia was associated with a prerenal (dehydration), a postrenal (obstruction of the left ureter), and an intrinsic renal component.

Are Upper Tract Uroliths Commonly Associated with Renal Failure?

Some of the factors influencing the biological behavior of upper tract uroliths are the following:

1. Mineral type
2. Involvement of one or both kidneys
3. Involvement of the ureters, urinary bladder, and urethra
4. Concomitant bacterial urinary tract infection, especially with uropathogens that produce urease
5. Rate of growth of existing urolith(s) and rate of formation of additional uroliths
6. Migration of urolith(s) from the kidneys into the ureter(s)
7. Size and number of the uroliths
8. Underlying cause(s) of the uroliths
9. Status of renal function
10. Concomitant unrelated disorders

CaOx nephroliths or ureteroliths that do not obstruct urine outflow and are not associated with bacterial UTI may persist for years in cats without substantial change in urinary tract structure or function. However, if persistent complete outflow obstruction is caused by a nephrolith or ureterolith, progressive deterioration of function of the affected kidney and marked hydronephrosis typically occur.

Obstruction of the ureter or renal pelvis of one kidney may not result in systemic clinical signs or azotemia, especially if the urinary tract is sterile and the contralateral kidney has adequate function. However, partial or total obstruction of just one ureter with a urolith may precipitate an acute onset of a uremic crisis in cats with compensated chronic renal failure (so-called "acute-on-chronic" renal failure).

In the unlikely event that complete obstruction of urine outflow through both ureters resulting from uroliths occurs suddenly in a cat with normal renal structure and function, severe hydronephrosis will not develop because death from uremia within a few days precludes severe anatomical changes in both kidneys. If uroliths obstruct urine outflow completely from a kidney in a patient with a concomitant bacterial UTI, acute pyelonephritis and life-threatening septicemia may result.

During recent years, CaOx nephroliths have been encountered with sufficient frequency in cats with chronic renal failure to warrant radiography or ultrasonography as a standard component of evaluation of cats with renal failure. In a study of cats with naturally occurring chronic renal failure currently in progress at the University of Minnesota Veterinary Teaching Hospital, nephroliths were detected unexpectedly by survey radiography in 13 of 20 cats with intrarenal azotemia. The etiological interrelationships of chronic renal failure in cats and CaOx nephroliths are not known. However, risks for both disorders may be linked, at least in part, to underlying disorders causing acidosis, hypercalciuria, and/or hyperoxaluria. A recent study in rats indicated that oxalate ions and CaOx monohydrate crystals stimulate inflammatory proteins.[3] By promoting hyperoxaluria and inflammatory mediators, oxalate ions could promote formation of CaOx uroliths and also affect kidney structure and function adversely. Further studies are needed to evaluate this hypothesis.

How Is Ureteral Obstruction Verified?

Factors to consider when developing a diagnostic plan to determine whether a urolith is obstructing a ureter include the sensitivity of the diagnostic procedure, the status of the patient's renal function, and the type of therapy (medical and/or surgical) being considered (Table 43-1). Although survey abdominal radiographs are valuable in providing an overview of the entire urinary tract and surrounding abdominal structures, they are not reliable for verification of partial or total obstruction of ureters with uroliths.

Intravenous urography is a sensitive method to detect ureteral obstruction in nonazotemic and mildly azotemic patients. Excretion of radiopaque contrast agent by the kidneys is dependent on adequate glomerular filtration. In patients with marked azotemia, reduced filtration of contrast media may impair visualization of the kidneys, ureters, and bladder. Compensatory strategies include increasing the dose of contrast media administered[4] and increasing the time of the procedure (i.e., additional radiographs obtained 2 to 4 hours after administration of contrast media). To minimize adverse events associated with intravenously administered contrast media, we recommend deficits in hydration be corrected before administration of such media. Adverse reactions to contrast media also can be minimized by use of nonionic iodinated contrast media (e.g., iothalamate meglumine).

To minimize the risk of contrast media–induced nephropathy, some clinicians have advocated transcutaneous antegrade contrast pyelography as an alternative to intravenous urography.[5] Contrast-enhanced pyelography provides a sensitive method of verifying the presence and location of ureteral obstruction. However, puncturing the renal pelvis to inject contrast media may reduce intraureteral pressure. Increased hydrostatic pressure proximal to the site of obstruction promotes movement of the urolith through the lumen of the ureter.[6] Therefore some patients may benefit from a delay in transcutaneous antegrade contrast-enhanced pyelography until noninvasive strategies to promote movement of stones through the ureter have been evaluated. However, in situations in which intravenous urography is likely to be unsatisfactory because of severe renal dysfunction (i.e., the patient is severely azotemic), transcutaneous antegrade pyelography should be considered. Additional discussion of antegrade pyelography and description of the technique can be found in Chapter 41.

As an alternative to contrast radiography for evaluation of severely azotemic patients, we recommend a combination of

Table 43-1 | **Medical Imaging of Cats with Nephroureteroliths**

METHOD	ADVANTAGES	DISADVANTAGES	RECOMMENDED USE
Survey radiography	Rapid detection of radio-opaque ureteroliths Assessment of kidney size Noninvasive	Cannot determine if ureteroliths are causing obstruction Feces in colon may obscure ureteroliths	Initial diagnostic test to localize azotemia, renomegaly, or other clinical signs referable to ureteroliths Monitor movement of radio-opaque ureteroliths
Intravenous urography	Localization of site of obstruction Subjective assessment of kidney function in nonobstructed kidney Diuretic action of contrast agent may augment ureterolith passage	Degree of renal/ureteral contrast enhancement is related inversely to the magnitude of azotemia Contrast-induced nephropathy is possible but recognized uncommonly	To confirm ureteral obstruction in nonazotemic or mildly azotemic cats that are well hydrated
Ultrasonography	Assessment of renal pelvic dilation Assessment of renal resistive index	May not localize the site of obstruction May be unable to visualize uroliths in the mid-portion or the distal portion of the ureter Pyelectasia is not synonymous with ureteral obstruction; other common causes for renal pelvic dilation include fluid administration and pyelonephritis	Corroborate with other evidence supporting ureteral obstruction in moderate to severely azotemic cats
Transcutaneous antegrade pyelography (via ultrasound-guided pyelocentesis)	Accurate localization of site of obstruction Urine obtained from the renal pelvis for analysis and culture Greatly minimizes risk of contrast media–induced nephropathy	Experienced ultrasonographer required Perirenal leakage of contrast agent Perirenal leakage of urine Puncturing the excretory tract may reduce intraureteral pressure and minimize the likelihood that ureteroliths will pass	Pyelocentesis has many benefits but also is associated with several risks. If a larger than expected tear in the excretory pathway is created, it may be associated with reductions in diuresis-induced hydrostatic pressure impairing ureterolith movement. We recommend that pyelography be performed to confirm and localize ureteral obstruction before surgical management.
Computerized tomography	Accurate localization of site of obstruction	Requires anesthesia	Localize and confirm the site and cause of ureteral obstruction. Although used routinely in human medicine, its role has not been investigated in cats with ureteroliths.

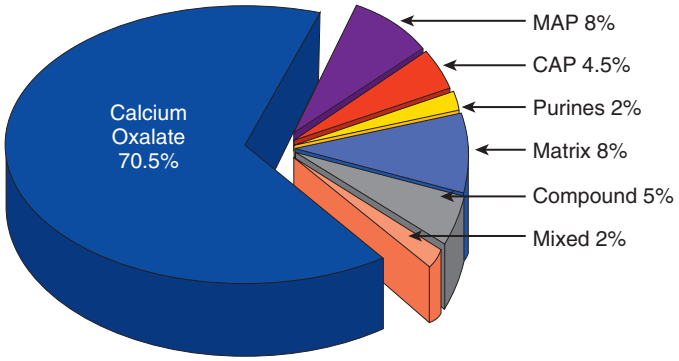

Figure 43-2. Distribution of the mineral composition of nephroliths and ureteroliths from 1599 cats whose stones were submitted to the Minnesota Urolith Center for quantitative analysis between 1981 and 2003. *MAP,* Magnesium ammonium phosphate; *CAP,* calcium phosphate.

survey radiography and ultrasonography. Ultrasound findings associated with obstruction of a ureter include a dilation of the renal pelvis, dilation of the ureter, and a high resistive index.

How Should This Patient Be Managed?

Selection of effective methods of treatment is based primarily on knowledge of ureterolith composition and size, the severity of renal failure, and the response to initial diuretic (i.e., fluid) therapy. Without the availability of uroliths for analysis, determination of urolith composition may be difficult. Although voiding urohydropropulsion could have been performed to retrieve uroliths from the urinary bladder of this patient, it was not. When the composition of a ureterolith is unknown, we recommend predicting mineral composition of uroliths based on results of the urinalysis, serum biochemical profile, and radiographic findings. We interpreted the findings of very radiodense uroliths in a cat with acidic urine to be CaOx. This interpretation is supported by the knowledge that the majority of nephroliths and ureteroliths submitted for analysis to the Minnesota Urolith Center (70.5 per cent, 1127 of 1599 cats) were composed of CaOx (Figure 43-2).

Is Immediate Surgical Removal of Ureteroliths Necessary?

The urgency for surgical intervention depends on the degree and progression of renal dysfunction, the potential for renal recovery, the potential for urolith migration through the ureter, the presence of infection or uncontrollable pain, and anticipated risks associated with surgery. If renal failure has deteriorated abruptly to the point that electrolyte abnormalities are persistent and life threatening, intervention to improve glomerular filtration by relieving urinary obstruction should be considered if the electrolyte abnormalities cannot be controlled by less invasive measures (e.g., fluid replacement, hemodialysis, peritoneal dialysis). Although placement of nephrostomy tubes may appear a logical and feasible method of bypassing the obstruction temporarily, maintaining nephrostomy tube position, seal, and patency for longer than 24 hours often is technically difficult.[7,8] In addition to severe unresponsive azotemia, if infection and pain cannot be managed appropriately, surgical ureterolith removal should be considered. Because of the high risk of irreparable ureteral damage associated with ureterotomy, ureterolith removal is not indicated if (1) ureteroliths are migrating through the ureter, (2) azotemia is resolving, (3) the associated kidney is nonfunctional, or (4) ureteral surgery is attempted by surgeons unfamiliar with appropriate techniques[7] (see Chapter 41).

CASE REPORT: DAYS 2 THROUGH 15

Initial therapy in our patient consisted of intravenous fluids (Normosol M, 30 ml/hr), cefazolin (120 mg IV q8h), and famotidine (2.7 mg IV q24h). After 24 hours, amlodipine (0.625 mg PO q24h) also was prescribed to promote smooth muscle relaxation of the ureter. By the sixth day, the patient's appetite had improved and serum creatinine concentration was approximately 50 per cent lower. The patient was discharged with instructions to feed canned food formulated for patients with renal failure and instructions to continue administration of amlodipine.

Three days after discharge (day 9), the patient returned to the hospital for acute lethargy and refusal to eat. Her serum creatinine had increased to 13.7 mg/dL. She received intravenous fluids followed by mannitol (1 gm/kg once) and then furosemide (1 mg/kg once) because of a presumptive diagnosis of acute, oliguric renal failure. Within 12 hours, urine production had improved and diuretics were discontinued. Famotidine and nasoesophageal feeding were the only additional therapies that this patient received, besides intravenous fluid support. After 7 days of hospitalized care (day 15), serum creatinine concentration was markedly reduced (3.7 mg/dL). Care after discharge included receiving 100 to 200 ml of sterile lactated Ringer's solution subcutaneously once a day. Amlodipine was discontinued.

Will Ureteroliths Pass into the Urinary Bladder?

In people, migration of ureteroliths into the urinary bladder is variable and influenced by their location and size. In a study of 378 human patients, ureterolith passage rates were higher for stones in the distal ureter (71 per cent) than for stones in the proximal ureter (22 per cent).[9] In another study, irrespective of location, 95 per cent of ureteroliths less than 2 mm in diameter passed in 31 days compared with 40 days for stones greater than 2 mm but less than 6 mm in diameter.[10] The time for ureteroliths to migrate into the urinary bladder of cats has not been evaluated systematically. Likewise, reliable protocols that favor ureterolith passage have not been adopted consistently. However, in a study of 11 cats with CaOx ureteroliths, follow-up medical imaging did not reveal antegrade ureteral migration 13 to 42 days after initial diagnosis.[11]

How Long Can We Wait and Watch?

The length of time that the feline kidney can tolerate complete obstruction and yet recover adequate function to maintain homeostasis is unknown. Studies in dogs found no recovery of renal function after 40 days of complete unilateral ureteral ligation.[12] However, adequate functional recovery from hydronephrosis did occur 153 days after accidental ureteral ligation in a 42-year-old woman.[13]

Compared with complete ureteral obstruction, impairment of renal function associated with partial ureteral obstruction may be relatively mild. For example, in dogs, partial ureteral

obstruction for 8 weeks decreased effective renal plasma flow by 50 per cent.[14] However, 8 weeks after relief of obstruction, effective renal plasma flow returned to normal. We have observed cats with unilateral ureteroliths in which serum creatinine concentrations remained stable over several years. Until reliable guidelines are established in cats, renal function and urolith migration should be evaluated periodically to determine when the risks of waiting outweigh the risks of surgery.

What Factors Promote Ureterolith Passage?

Factors likely to influence the migration of uroliths through the ureter include (1) the size and shape of ureteroliths, (2) inherent areas of narrowing of the ureteral lumen, (3) hydrostatic pressure of urine proximal to the ureterolith, and (4) ureteral spasm, inflammation, and edema at the site of the urolith. Although some of these factors can be modified so that ureterolith migration is enhanced, prospective studies are needed to determine which factors are important and which therapies are effective and safe for cats (Table 43-2). For example, in human beings, extracorporeal shock-wave lithotripsy is used commonly to shatter ureteroliths successfully into smaller fragments that can pass through the ureter.[15] However, feline kidneys appear to be more susceptible to shock-wave lithotripsy damage.[16] Decreasing the energy and frequency of shock waves would appear to be a logical solution to minimize parenchymal damage to kidneys. However, the recent observation that CaOx uroliths in cats are less susceptible to shock-wave fragmentation than CaOx uroliths in dogs suggests that more energy is needed to fragment feline CaOx ureteroliths.[17] In search of safer methods of ureterolith fragmentation, the type of lithotriptor also may be a factor.[18] As newer generation extracorporeal lithotriptors with narrower focus beams become available to veterinary patients, adverse effects may be minimized. Additional discussion of lithotripsy for feline urolithiasis is found in Chapter 44.

Increasing the hydrostatic pressure proximal to the uroliths appears to be an important factor in facilitation of their passage through the ureter.[6,19,20] This hypothesis is based on studies in rabbits that evaluated ureteral transit time of 2 mm artificial concretions with and without holes.[6] Average transit time for concretions with holes was 29 days, compared with 5 days for concretions without holes. These results provide the basis for providing intravenous or subcutaneous isotonic fluid administration to promote the passage of stones in cats. Administration of osmotic diuretics (e.g., mannitol) and loop diuretics

Table 43-2 | **Agents That May Augment Movement of Ureteroliths**

DRUG	MECHANISM	DESIRED RESPONSE	COMMENTS	EMPIRICAL DOSE
Fluid administration	Diuresis	Increase ureteral hydrostatic pressure	Selection of appropriate type of fluid and selection of appropriate route and rate of administration provide a favorable risk/benefit ratio Avoid excessive potassium supplementation in normokalemic or hyperkalemic cats Monitor body weight to prevent overhydration	Typically 10 to 25 ml/kg/hr IV, or 100 to 200 ml/cat SC daily
Mannitol	Diuresis	Increase ureteral hydrostatic pressure	Effective strategy to increase urine volume Preferably give in conjunction with intravenous fluids Do not administer until deficits in hydration are corrected	0.5 to 1 g/kg (20 per cent solution) over 20 min q6-8h
Buprenorphine	Opiate agonist/ antagonist	Analgesia	Other opiates (e.g., butorphanol 0.1 to 0.5 mg IV, IM, SC, PO q4-6h) also should provide sufficient analgesia	0.01 mg/kg sublingually q12h
Amlodipine	Calcium-channel blocker	Ureteral relaxation	Efficacy and safety unknown in cats Systemic vasodilatation may further reduce GFR	0.625 mg/cat daily PO
Nifedipine	Calcium-channel blocker	Ureteral relaxation	Efficacy and safety unknown in cats Studies in human beings demonstrate efficacy	Doses to promote ureteral relaxation have not been determined
Tamsulosin	α-adrenergic antagonist	Ureteral relaxation	Efficacy and safety unknown in cats Studies in human beings demonstrate efficacy	Doses to promote ureteral relaxation have not been determined
Glucagon	Polypeptide hormone	Ureteral relaxation	One study in cats did not demonstrate efficacy; adverse effects occurred We do not recommend its use	0.05 to 0.1 mg/cat IV
Prednisone	Anti-inflammatory	Reduce ureteral inflammation and edema	Efficacy and safety unknown in cats Studies in human beings demonstrate efficacy for patients with acute obstruction	4 mg/kg daily PO
Dexamethasone	Anti-inflammatory	Reduce ureteral inflammation and edema	Efficacy and safety unknown in cats Studies demonstrate efficacy for human patients with acute obstruction	0.125 to 0.5 mg/cat IV or IM daily
Meloxicam	Nonsteroidal anti-inflammatory	Minimize inflammation and analgesia	NSAIDs are contraindicated in patients with renal insufficiency because they may cause renal ischemia	0.1 to 0.2 mg/kg q72h
Enalapril	Angiotensin-converting enzyme inhibitor	Reduce interstitial expansion and fibrosis	The renin-angiotensin system promotes progressive interstitial fibrosis in rats with ureteral obstruction Efficacy and safety unknown in cats	0.25 to 0.5 mg/kg q12-24h

(e.g., furosemide) also may increase proximal ureteral hydrostatic pressure beneficially by augmenting urine volume. However, to avoid adverse renal effects, cats should be hydrated adequately before, during, and after diuretic administration. Likewise, monitoring (e.g., body weight, central venous pressure) is important to ensure that patients do not become morbidly overhydrated.

In addition to increasing urine output, administration of medication to decrease ureteral spasm, edema, and inflammation improved stone expulsion rate and decreased expulsion time in human patients with distal ureteral stones. In one study, patients were randomized into three treatment groups.[21] The first group received nifedipine, a calcium-channel blocker, and deflazacort, a corticosteroid. The second group was treated with tamsulosin, an α-adrenergic antagonist, and deflazacort. The third group served as a control receiving no medication (except analgesics); however, all groups were instructed to consume a minimum of 2 liters of fluids daily. Only 43 per cent of patients in the control group expelled ureteroliths, compared with greater than 80 per cent of patients receiving additional therapy.[21]

Relaxation of the ureter in the region of the urolith and distal to the site of obstruction would appear logical; however, selection of appropriate treatment may be difficult because little is known about the physiological events that occur during ureteral obstruction in cats. Studies in anesthetized dogs demonstrated that glucagon (22 μg/kg) infusions reduced ureteric contractions significantly.[22] Anecdotal evidence of its beneficial use in human beings to relieve ureterolith colic has spawned interest in its use to promote ureterolith movement in cats. However, preliminary data in one study of cats receiving glucagon (0.05 to 0.1 mg) did not demonstrate significant efficacy.[23] A less-than-favorable outcome might have been expected, because glucagon also may reduce hydrostatic forces propelling the urolith distally. In an experimental study in dogs, intraureteral pressure proximal to the site of obstruction was 43 per cent lower during glucagon infusion.[22] In addition, glucagon infusion at therapeutic doses creates some risk. In cats with ureteroliths, several animals experienced transient vomiting, diarrhea, tachypnea, and dyspnea after glucagon administration.[23]

Amitriptyline, a tricyclic antidepressant, which has been recommended to manage a variety of urinary tract signs in cats, may induce ureteral smooth muscle relaxation. In ex vivo studies using human and pig ureteral segments, amitriptyline partially inhibited contractile activity at a concentration of 0.1 μmol/L, and completely inhibited contractile activity at a concentration of 1 μmol/L.[24] In this same study, the authors demonstrated resolution of naturally occurring urethral obstruction within 72 hours of cats receiving amitriptyline (1 mg/kg/day). Although the authors attributed this result to smooth muscle relaxation, only the urethra proximal to the prostate has appreciable amounts of smooth muscle.[25] No further clinical recommendations can be made regarding amitriptyline in the management of feline ureteroliths at this time.

CASE REPORT OUTCOME: DAYS 17 THROUGH 33

The patient was monitored at 2, 4, 9, and 18 days (days 17 to 33) after the last discharge from hospitalization. During that time, serum creatinine increased initially (from 3.7 mg/dL to 6.6 mg/dL) but the patient did not require hospitalization. The ability to avoid hospitalization may have occurred in part because of continued subcutaneous administration of isotonic fluids at home (approximately 200 ml a day). Radiography on this day revealed that stones had migrated further down the ureter but also that stones originally in the kidney had now moved into the ureter (Figure 43-3).

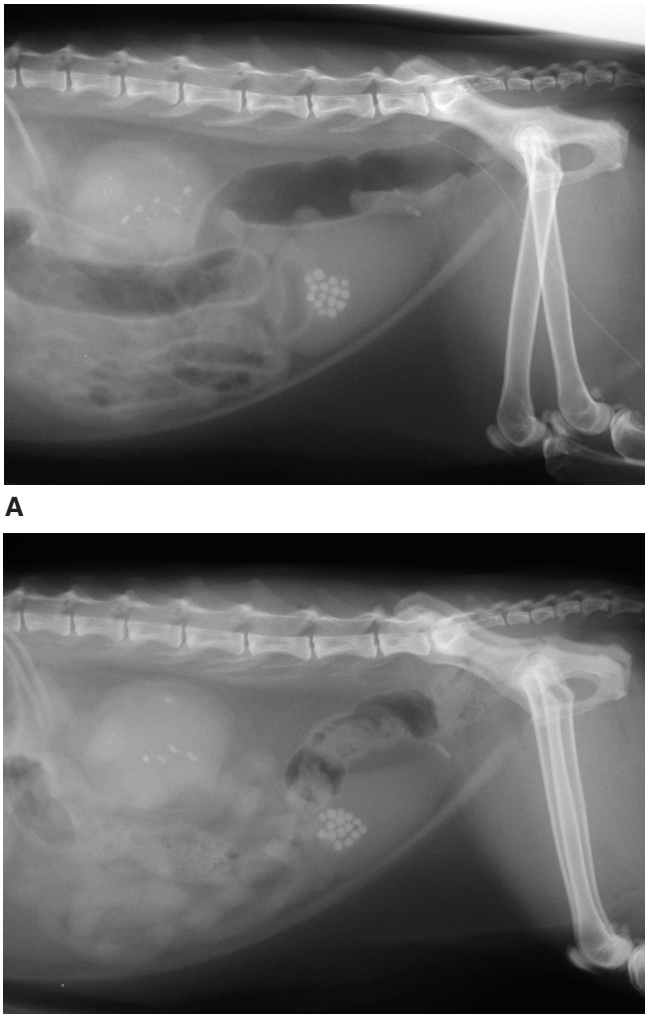

Figure 43-3. Survey lateral radiographs of the cat described in Figure 43-1. These radiographs were obtained 13 **(A)** and 17 **(B)** days after initiation of therapy, and document the migration of uroliths through the ureter and into the urinary bladder. During this period, several nephroliths also migrated into the ureter.

Nine days after the second hospitalization (day 24), the serum concentration of creatinine was almost normal (2.4 mg/dL). Survey radiography was not performed at this time; however, radiographs obtained a little over one week later (day 33) revealed that multiple ureteral stones had passed into the urinary bladder (Figure 43-4). Interestingly, the left kidney, which was originally 2.65 times the length of the second lumbar vertebra, was now a third smaller (1.96 × L2) and serum creatinine concentration had remained relatively low (2.2 mg/dL). Because stones in the urinary bladder were not causing clinical signs, they were not removed.

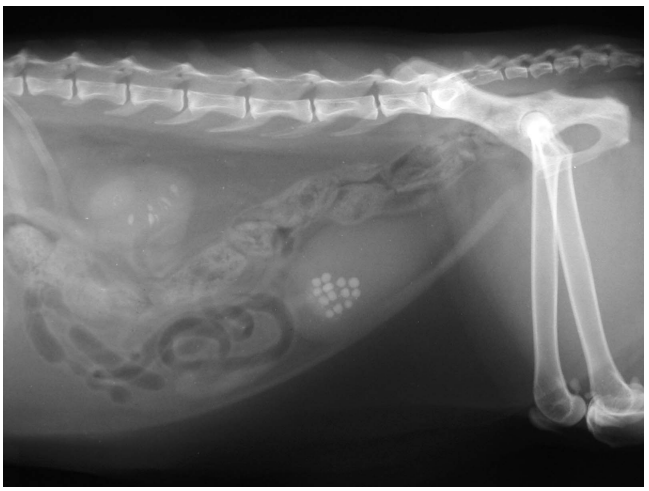

Figure 43-4. On day 33, the uroliths have moved into the urinary bladder. The left kidney was one third smaller, and the patient's serum creatinine concentration was reduced from previous measurements (2.2 mg/dL).

How Can Ureteroliths Be Prevented?

Minimizing the recurrence of ureteroliths requires knowledge of the mineral composition of the stone and an understanding of the factors responsible for its formation. Because the majority of ureteroliths in cats are composed of CaOx, the following pertains primarily to prevention of this stone type.

Although formation of CaOx uroliths is associated with a complex and incompletely understood sequence of events, several key factors are evident. Cats with CaOx uroliths are hypercalciuric compared with normal cats[26] (see Chapter 17). Results of epidemiological studies support the hypothesis that urine-acidifying diets designed to minimize magnesium-ammonium-phosphate urolith formation may have increased the occurrence of CaOx uroliths inadvertently by inducing or promoting hypercalciuria and possibly reducing citrate in the urine, an inhibitor of CaOx crystalluria.[27,28] Deficiencies in vitamin B6 promote excessive urine oxalate excretion and therefore should be avoided.[29] In addition, cats fed diets with low protein, potassium, or moisture were at increased risk for CaOx urolith formation.[27]

Crystal formation and subsequent crystal growth are a reflection of urine supersaturation for CaOx.[30] Therefore therapeutic methods that reduce urine calcium concentration and urine supersaturation with calculogenic substances should minimize urolith recurrence. Controlled studies to evaluate the efficacy of dietary modification in reduction of the recurrence of feline CaOx uroliths have not been reported. However, studies of cats with a history of CaOx uroliths revealed that current dietary recommendations reduced the magnitude of supersaturation of their urine with CaOx significantly as measured by urine activity product ratios.[26] Diets with high moisture content are preferred over dry formulations because the diuresis associated with increased fluid intake minimizes the concentration of calculogenic substances in urine and promotes more frequent evacuation of urinary crystals that may form. Detailed discussion of the influence of diet in cats with CaOx urolithiasis is presented in Chapter 46.

Are Cats with Nephroliths Likely to Develop Ureteroliths?

The previous case supports the hypothesis that nephroliths are a source for ureteroliths. However, the frequency with which kidney stones migrate into ureters and factors responsible for their movement are unknown. Our clinical impression is that the majority of nephroliths remain in the kidney. However, many urocystoliths perhaps resided originally in the kidneys. Likewise, small stones may pass through the entire urinary tract without clinical detection. Because of the likelihood that surgery and subsequent healing reduce kidney function, we generally do not recommend removing nephroliths on the chance they may obstruct the ureter at a future date.

UNANSWERED QUESTIONS

1. Why are uroliths common in the kidneys and ureters of cats and human beings and yet recognized uncommonly in dogs?
2. What is the association between renal failure and CaOx nephroureteroliths? Increased concentrations of oxalate are a risk factor for both urolith formation and renal damage. Do CaOx crystals adhere only to damaged renal tubular cells, or do CaOx crystals damage renal tubular cells, which promotes crystal adherence?
3. Is ureteral obstruction by uroliths a chronic progressive disease or an acute disease in most cats? This question is important for several reasons. In acute disease, antiinflammatory drugs may be indicated to reduce ureteral swelling and edema. In chronic disease, attempts to correct swelling and inflammation of the ureter are less likely to be effective.
4. What conditions and medications promote ureterolith migration in cats?
5. Under what conditions do the benefits of surgical removal of ureteroliths outweigh the risks?
6. Are angiotensin-converting enzyme (ACE) inhibitors indicated to preserve kidney function and structure in cats with ureteral obstruction? This question is important because experimental studies indicate that ureteral obstruction promotes interstitial fibrosis that is mediated through the renin-angiotensin system.[31]
7. What beneficial role could shock-wave lithotripsy or endoscopic laser lithotripsy have in the management of ureteroliths? Recall that the move to less invasive procedures in human beings with ureteroliths has improved renal preservation by a factor of 10.[2]

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Chapter 44

LITHOTRIPSY

India F. Lane, Mary A. Labato, and Larry G. Adams

With the increased prevalence of calcium oxalate urolithiasis in cats, the prevalence of upper tract urolithiasis also has increased dramatically. Upper tract uroliths in cats present a unique set of challenges, as reflected by the content of several other chapters in this text (see Chapters 41, 43, and 46). First, a conservative approach to these cases is preferred because manipulation of the feline kidney or ureter potentially is dangerous and requires advanced expertise. Fortunately, many nephroliths are slow to develop, slow to grow, and may remain static for long periods of time. Nonobstructive ureteroliths may be asymptomatic and pass into the lower urinary tract with conservative management and time.

Additionally, significant structural and functional renal damage has occurred already in many cats with urolithiasis, another factor that must be considered when making decisions regarding management. With diseased kidneys, additional insults must be avoided, especially if a single kidney is providing most or all of the renal function. Whether removal of existing uroliths has any impact on progression in chronically diseased kidneys is unknown. On the other hand, our experience with obstructive ureteroliths highlights the fact that these mobile uroliths pose pertinent threats to the renal function and long-term survival of cats. Clearly, significant damage develops without detection in many affected cats; preventing further damage should be a goal of feline practice.

Because of the risks of surgical manipulation of the upper urinary tract, noninvasive methods are attractive options for removal of nephroliths and ureteroliths in cats. The advent of extracorporeal shock wave lithotripsy (ESWL) revolutionized the management of urolithiasis in human beings[1,2]; interest in the technology currently is slowly creating a similar revolution in dogs.[3-7] The application of lithotripsy to the problem of feline urolithiasis has been an intriguing idea for some time, especially because the technique has proven so successful in dogs.[3] Renewed interest in feline lithotripsy has appeared with the acquisition of lithotriptors at other veterinary centers and with the rapid surge in feline nephroliths and ureteroliths. Although experience with ESWL in cats has been growing slowly and specific applications are likely to be useful in cats, the "silver bullet" for eliminating feline upper tract uroliths remains elusive. This chapter reviews lithotripsy methods applied in small animals, the unique challenges and questions relevant to feline practice, and current recommendations based on our combined experience.

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY METHODS

Lithotripsy refers literally to the "breaking of stones" and encompasses a wide range of ballistic, shock wave (SW), and laser energy methods applied to various stones and tissues. Veterinary urologic applications include primarily SW and laser methods, although mechanical (ballistic) instruments have been used in large animals. Stone types amenable to ESWL include urate, struvite, and calcium oxalate dihydrate uroliths. Calcium oxalate monohydrate and cystine stones are more resistant to SW fragmentation.[8]

Successful shock wave lithotripsy requires a source to generate SW, a method for focusing the SW to a solitary point, and a method for transmitting ("coupling") the SW to the patient (Table 44-1 and Figures 44-1 and 44-2). With extracorporeal methods, the SW are generated outside the body then reflected to converge on a target focal point (the urolith) in the patient (see Figure 44-1). Shock waves are high-amplitude sound waves generated by electrohydraulic, electromagnetic, or piezoelectrical energy sources. Like ultrasound waves, SW travel through media of fluid or soft tissue density until reaching a tissue interface at the "hard" acoustic surface of the urolith. Energy reflection and creation of tensile stresses along the surface of the stone, in addition to generation of cavitation bubbles within the stone, lead to fragmentation with repeated SW.[9,10] Simple dynamic fatigue of the stone after repetitive SW also contributes to collapse of the stone.[10]

The initial lithotriptor modified for human clinical use, the Dornier HM3 (Dornier, Marietta, GA) relied upon transmission of SW through a water bath medium, which required the patient to be partially submerged during treatment ("wet" lithotripsy). An electrohydraulic electrode created pulsatile sparks, which generated shock waves.[1-4] Newer lithotriptors use other SW generators and "dry" methods, in which SW are coupled to the patient through a fluid-filled cushion while the patient lies on an adjacent plastic cradle (see Figures 44-1 and 44-2).[11,12]

Table 44-1 | **Features of Extracorporeal Lithotriptors Employed in Veterinary Patients**

MODEL	MANUFACTURER	SOURCE	FOCUSING	COUPLING	IMAGING	FOCAL ZONE	PEAK PRESSURE
HM-3	Dornier	EHL	Ellipsoid	Water bath	Radiograph	15 × 90 mm	1300 bar
Modulith	Storz	Electromagnetic	Parabolic	Water cushion	Rad/US	6 × 30 mm	1000 bar
MFL-5000	Dornier	EHL	Ellipsoid	Water cushion	Rad/US	10 × 40 mm	1000 bar
Piezolith 2500	Wolf	Piezoelectric	Concave dish	Water cushion	Rad/US	1.5 × 11 mm	1200 bar
Lithostar II	Siemens	Electromagnetic	Acoustic lens	Water cushion	Rad/US	6 × 80 mm	500-800 bar

EHL, Electrohydraulic; *Rad/US,* Both radiographic (fluoroscopic) and ultrasonographic imaging modalities available.

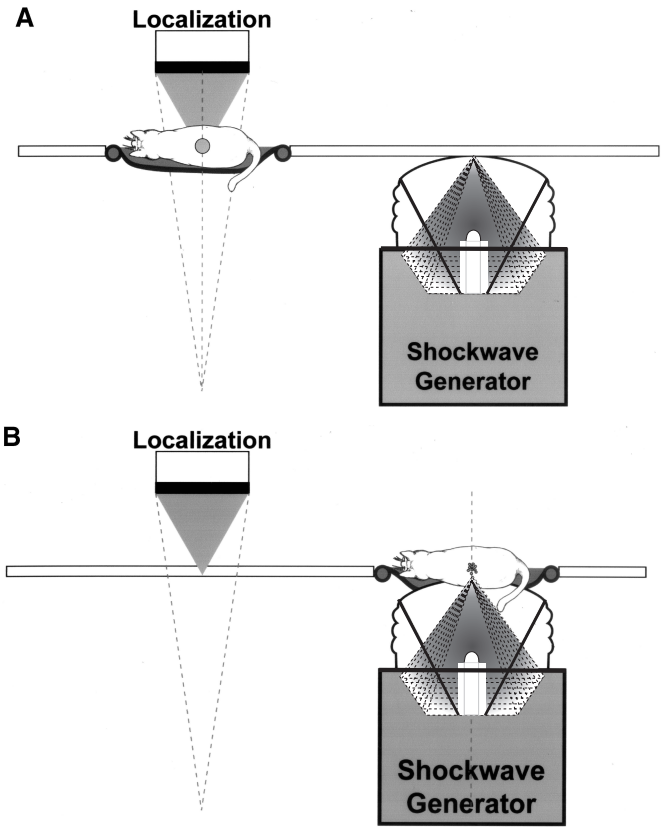


Figure 44-1. Schematic illustration of dry extracorporeal shock wave lithotripsy. **A,** Focusing position under mobile C-arm fluoroscopy. **B,** Treatment position, with focused shock waves originating from electromagnetic source.

Figure 44-2. Anesthetized cat positioned on the Dornier MFL-5000 cradle and cushion for application of shock waves.

Dual-imaging capabilities, with both fluoroscopic and ultrasonographic tracking of uroliths, and variable power settings are additional features of newer lithotriptors.[12] Although these lithotriptors are easier to use and to maintain, the efficacy of dry lithotriptors is lower than that of the "gold standard" water bath model because of a smaller focal zone and in some cases, lower peak pressure. This narrow focal zone limits SW damage to surrounding tissues but demands greater precision in targeting uroliths. Early experience with a second-generation unit (Storz Modulith SL 20, Karl Storz, Atlanta, GA) in dogs appears to yield similar results; a higher retreatment rate may be expected.[6,7]

The latest (so-called "third") generation of lithotriptors is designed to increase portability and flexibility in treatment method. Machines with mobile, handheld SW application sources may be useful for reaching uroliths in difficult locations, and may allow for nonurologic applications (e.g., orthopedic) to be delivered by the same lithotriptor. Newer machines also are designed to be smaller and less costly than prior lithotriptors.[12] However, these lithotriptors sacrifice efficiency and depth of penetration, which limits their effectiveness for nephroliths in larger human patients. A decreased depth of penetration may not be problematic for cats and smaller dogs, if efficacy can be maintained. However initial experience with the handheld units suggests that efficiency is sacrificed; a higher number of shocks and a higher retreatment rate are likely.

In general, ESWL treatment includes general anesthesia of the animal, localization of the urolith in the lithotriptor's focal zone, and application of sets of SW until sufficient fragmentation is observed on subsequent imaging (Figures 44-3 and 44-4). Sonographic imaging is ideal for continuous monitoring of stone fragmentation and is less costly than fluoroscopic monitoring systems. However, sonographic visualization during lithotripsy requires a highly skilled operator in human practice and has proven difficult in small animals. Even with fluoroscopic or hard copy images obtained during treatment, assessing degree of fragmentation immediately can be difficult, because fragments may overlie each other until they begin to move into the ureter. Bilateral uroliths can be treated during the same anesthetic episode unless concern about individual renal function dictates staged treatments.

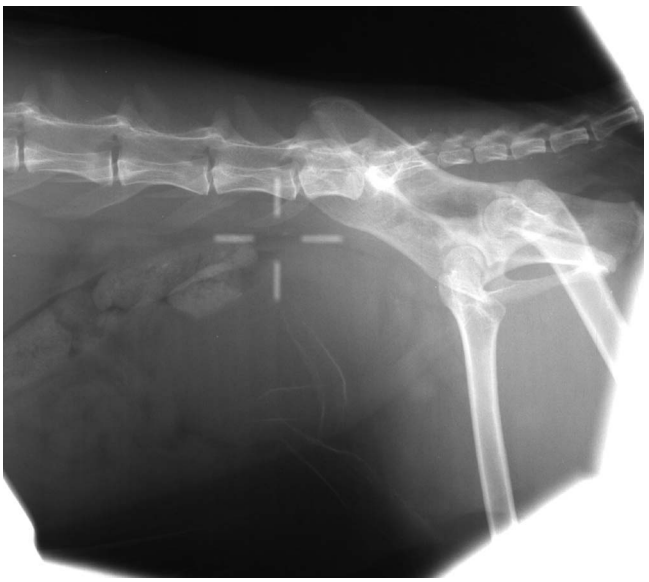
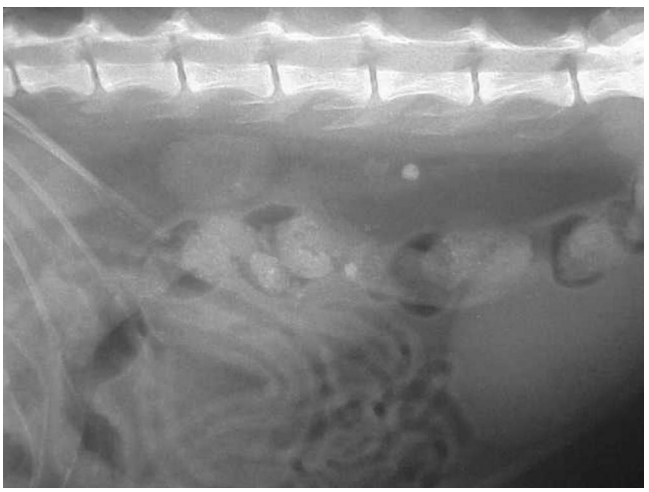
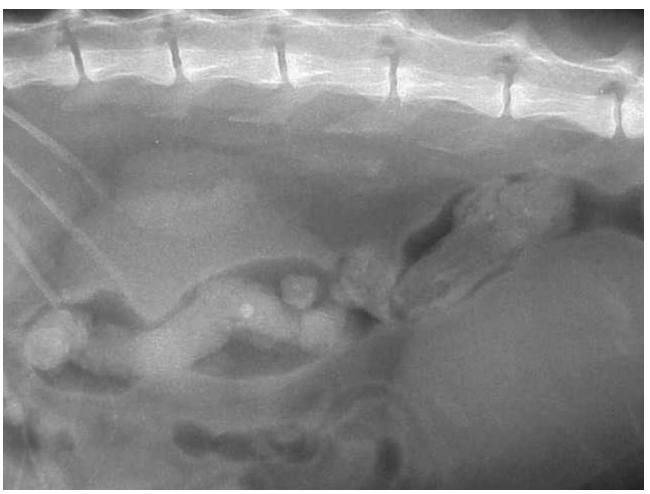


Figure 44-3. Radiographic appearance of distal feline ureterolith positioned in the F2 focal zone of the Storz Modulith SL20 for application of shock waves.



A



B

Figure 44-4. Lateral radiograph illustrating fragmentation of a ureterolith with the Dornier MFL-5000. **A,** Pretreatment. **B,** Radiographic appearance after 2000 SW.

After treatment, a period of diuresis (2 to 4 days) is continued to aid in fragment passage. Follow-up radiographs and ultrasound generally are completed a day or two after treatment and every 3 to 4 weeks thereafter. Urolith passage may be rapid in some animals or may take several months to completely clear from the urinary tract. Many canine and human nephroliths require a second treatment to gain optimal fragmentation. Fragmentation is considered complete in human beings when only clinically insignificant (smaller than 2 mm) fragments remain visible.[13] However, the wisdom of this recommendation is under revision. Residual fragments are now considered likely to cause symptomatic episodes in the future, to serve as a nidus for ongoing infection, or to act as scaffolding for recurrent growth of nephroliths. A stone-free patient is certainly the preferred outcome in human and probably veterinary patients.[10]

ESWL is contraindicated in animals with uncontrolled coagulopathy, hypertension, or other intraabdominal disease such as chronic pancreatic or hepatic disease. Concurrent pyelonephritis or renal failure, although considered an indication for pursuing treatment of nephroliths, may increase the risk of SW-induced renal injury in dogs and cats. Urinary tract infection should be managed and sterile urine obtained before ESWL. Although small body size is not a contraindication, a greater percentage of the kidney is exposed to SW injury in patients or species with small kidneys. The risk of damage to surrounding tissues, including lungs and bone, also is greater in very small animals.

Potential complications of ESWL include renal parenchymal hemorrhage, subcapsular hematoma formation, obstruction with fragments, arrhythmias, transient or permanent renal impairment and, rarely, acute renal failure.[3,10,14] Extrarenal damage to pancreas, lungs, liver, muscle, and bowel also is possible but usually resolves quickly.[10] Acute pancreatitis has been reported in human and canine patients.[15,16]

VETERINARY EXPERIENCE WITH EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

After its success in dogs, ESWL application in cats was investigated initially in the mid 1990s. Using the Dornier HM-3 lithotriptor, ESWL (1000-1500 SW, 14 kV, 2 Hz) appeared to create disproportionate renal hemorrhage and renal impairment in healthy cats when compared with dogs.[3] Based on these results, limiting the SW dose (to 750 SW at a 13 kV energy level) appeared prudent. For comparison, canine nephroliths usually are treated with 750 to 1400 SW generated at 13.5 to 15 kV, with a high success rate.[3] The outcome in clinically affected cats also was discouraging, with fragmentation of nephroliths and ureteroliths insufficient to facilitate passage through the tiny feline ureter. Using the HM-3 lithotriptor, spontaneously occurring ureteroliths could be fragmented successfully in only one of five cats. Partial fragmentation of upper tract uroliths was achieved in two additional cats, but fragments were not small enough to move down the ureter. In addition, transient or permanent worsening of renal function occurred in three cats after ESWL, with increases in serum creatinine observed within 24 hours.[3] Conclusions at that time reflected the ongoing "catch 22" for treating cats with nephroliths or ureteroliths: more powerful lithotripsy protocols were necessary to treat feline uroliths adequately, yet these protocols were likely to create unacceptable renal damage in the process.

Since these early results, limited success has been observed at other sites using "dry" lithotriptors in cats. Gonzales, Labato, Solano, et al recently investigated the effects of dry lithotripsy on the kidneys in four healthy cats.[17] Using a Dornier MFL-5000 (Dornier Med Tech America, Inc, Kennesaw, GA) lithotriptor, 2000 SW were applied to the kidney at a energy level of 24 kV. The SW dosage chosen for the study was extrapolated from studies in dogs and minipigs and reflects current treatment recommendations in human patients. The dose appeared to be well tolerated in these healthy cats. Transient hematuria was observed in two of the four cats over the initial 48-hour period after ESWL treatment. None of the cats displayed any signs of discomfort or stranguria after the procedure. The investigators found no significant effects on ultrasonographic appearance of the kidneys at 24 hours and 14 days post treatment. Additionally, no difference existed in pretreatment and 14-day posttreatment glomerular filtration rate measurements in these cats.[17] Although tissue was not evaluated microscopically in these cats, the results are promising evidence that certain ESWL protocols may not damage renal function in healthy cats. However, this shock wave dosage still may not be adequate to fragment feline uroliths sufficiently and may have different results in diseased kidneys. The effects of multiple ESWL treatments on the feline kidney and the long-term effects of such protocols also are unknown. Furthermore, the most pronounced effects on renal function appear to occur within hours following SWL, a time period that was not fully assessed in this study.

Two cats with partially obstructive ureteroliths have been treated using this Dornier MFL-5000 lithotriptor. High SW doses (2400 SW at 24 kV) were applied. Fragmentation of ureteroliths was observed fluoroscopically; however, some fragments did not advance down the ureter to the urinary bladder despite aggressive diuresis. There were no changes in short-term renal function, or any other apparent adverse effects, in the treated cats.

Obstructive ureteroliths have been fragmented successfully in two of three cats with use of another dry lithotriptor, the Storz Modulith SL20 (Karl Storz, Inc., Atlanta, GA).[18] High SW doses were applied in these cats because the ureteroliths were separated from the kidneys by several centimeters. Although renal injury was considered less likely, treatment was still difficult because the ureteroliths provided very small targets for SW. In one cat, two treatments of approximately 3500 SW (16-18 kV, 2 Hz) were applied before gaining sufficient fragmentation; in the other cat, a smaller distal ureterolith was fragmented successfully and passed after one treatment of 3000 SW (16-18 kV, 2 Hz). In the latter two treatment sessions, SW were applied only between respirations (under controlled ventilation) to minimize movement of the urolith during SW application. No significant adverse effects were observed, although increased obstruction was observed between treatments in the cat that required two treatments. Azotemia was reduced after ESWL in all three cats.

I* currently am evaluating the efficacy of a smaller, handheld lithotripsy unit for ureterolith fragmentation. It appears that greater SW exposure is necessary to result in adequate fragmentation with this lithotriptor. With any lithotriptor, multiple treatments seem likely to be necessary for successful ureterolith fragmentation in some cats.

*One of the chapter co-authors, Mary A. Labato.

SPECIAL CHALLENGES IN CATS

A number of issues influence the decision to consider lithotripsy for feline uroliths (Table 44-2). First and foremost, many uroliths do not require intervention; a "watchful waiting" monitoring period can be undertaken instead. A thoughtful discussion of conservative versus aggressive approaches to upper tract nephroliths is provided in Chapter 43. On the other hand, clinicians and cat owners sense intuitively that untreated uroliths must be disadvantageous to renal health in the long term. Illustrative of the devastating effects of some uroliths, the intensity of acute ureteral obstruction is reflected in Chapter 41.

Second, the occurrence of multiple upper tract uroliths in an individual cat increases the complexity of treatment decisions. Unfortunately, many cats with uroliths appear to be remarkable "stone factories," with mineralized opacities identified in multiple sites at the time of diagnosis. Unless an obviously obstructive urolith is present, it can be difficult to determine which urolith is the primary problem at any given presentation. Furthermore, nephroliths often are multiple and scattered throughout the renal pelvis and parenchyma in affected cats; several ureteroliths may be lined up along one or both ureters. This stone burden can be so great that prolonged and extensive ESWL would be required to provide significant benefit to the patient. Stone burden (number and size of stones) is correlated inversely with success of ESWL in human patients.[10]

However, when faced with renal pelvic or ureteral obstruction in a cat, often located in a single or majority functioning kidney, intervention is necessary and surgical options are not particularly attractive. ESWL may be a reasonable option for a single nephrolith or a small group of localized uroliths contributing to urinary tract signs (e.g., urinary tract infection, hematuria, renal failure, or discomfort). However, if multiple uroliths (especially ureteroliths) are encountered, the most distal ureterolith must be fragmented first, followed by the next most distal, and so on, to ensure free passage of all fragments.

Table 44-2 | **Clinical Considerations Regarding Extracorporeal Shock Wave Lithotripsy in Cats**

Do the uroliths require direct treatment or can they be monitored for progression or movement?
Can a single stone or small group of stones be identified as the primary problem?
Will an immediate benefit result from urolith removal in the patient (i.e., relief of obstruction, removal of infectious nidus, relief of pain)?
Will a long-term benefit (e.g., protection of renal parenchyma, renal function, ureter) result from urolith removal?
Does the risk posed by the urolith outweigh the risk of potential damage created by ESWL?
Is damage to other diseased tissues (e.g., from chronic pancreatic or hepatic disease) a risk?
Are ureteroliths separated from the renal pelvis by 1 or more centimeters?
Are ureteroliths clearly identifiable on survey radiographs so that they can be located readily during ESWL?
Can the cat tolerate general anesthesia and fluid diuresis post treatment?
Are concurrent problems such as chronic renal failure and hypertension well controlled?
Are surgical or ESWL retreatments readily available for an obstructive fragment?

When ESWL treatment is undertaken, fragmentation of feline uroliths into pieces small enough to pass into the lower urinary tract can be difficult. The fragility of canine and feline uroliths has been investigated in vitro, using intact calcium oxalate uroliths (seven feline, seven canine) submitted to the Minnesota Urolith Center.[19] Using a research electrohydraulic lithotriptor that simulates the function of the Dornier HM3, breakage of the stones after 100 SW at 20 kV was evaluated using change in digital image size. In this study, significantly less breakage was observed in feline stones than in canine uroliths paired for size and composition,[19] which confirms the clinical impression that feline uroliths behave in a unique fashion when compared with those of other species. In some of the calcium oxalate monohydrate and monohydrate/dihydrate mixed uroliths, additional internal structure or layering was evident in the canine uroliths, which may increase their breakability. Microcomputed CT appearance of the four pairs of calcium oxalate dihydrate uroliths, however, was similar between the two species.[19]

Compounding the difficulty in fragmenting feline uroliths is the need to achieve exceptionally fine fragments. The feline ureteral lumen is extremely small (0.4 mm internal diameter), so urolith fragments must be small to pass into the urinary bladder. Additionally, uroliths that appear to traverse the ureteral length could later obstruct the male cat urethra. In dogs, a low-power, low-frequency but high-SW number protocol appears to create the smallest "dustlike" fragments. Low energy levels, although preferred in cats, have not proven effective in fragmenting ureteroliths and may not be effective for large nephroliths.

Whether the feline kidney will withstand the high number of SW that may be required is unknown. The potential for renal injury also appears greater in cats than in other species. Renal injury associated with ESWL has been well characterized in canine and porcine kidneys and is influenced by SW dose (number and energy), rate of application, and renal size.[20-27] Acutely, contusion, edema, hematoma, and microvascular trauma can be expected after lithotripsy in most treated animals. Vasoconstrictive responses in the treated and untreated kidney can lead to decreased renal blood flow and glomerular filtration rate. Nephron damage can be seen near the focal zone also, including cellular damage, tubular dilation, and mild tubular necrosis.[20,21] Most of these effects are dose (SW number and energy level) dependent, but some individuals appear to be at greater risk. The risk appears to be greater in juvenile animals and animals with small renal size.[10] In both circumstances, a greater percentage of the small kidney is subjected to SW trauma.[24,25] In human beings, age and uncontrolled hypertension are additional risk factors. Pyelonephritis also may potentiate ESWL injury.[26] Chronically, fibrosis, calcification, nephron loss, and scarring in the region of ESWL may be expected, and have been identified in canine subjects.[27] In human patients, progression of systemic hypertension and an increased rate of stone recurrence also are long-term concerns.[10]

In cats, small renal size and an inherent sensitivity of feline kidneys to insults may heighten the potential for short-term and long-term injury. Furthermore, cats with renal disease and urolithiasis often are older, hypertensive, and may have chronic renal inflammation. Advances in feline lithotripsy require additional study of bioeffects in this species. Advanced imaging modalities such as MRI or CT, additional studies of renal blood flow and GFR in treated cats, and long-term assessments will define the safety of ESWL protocols.

Although direct insult to the kidney is avoided in treatment of ureteroliths, the small size and location of feline ureteroliths often pose a challenge to the efficacy of ESWL. Clear imaging and accurate focusing of ureteroliths may be more difficult because of their small size and the interference of various overlying tissues and are especially difficult if ultrasound is the primary imaging modality employed. Careful positioning of the stone is required to maximize SW contact with ureterolith surfaces (see Figures 44-3 and 44-4). Lithotripsy fragmentation of ureteroliths is more difficult than nephroliths for several other reasons. During lithotripsy, the ureterolith fragments may adhere to the ureteral mucosa and will not fall away immediately from the original site, which diminishes the effectiveness of subsequent SW.

Impacted ureteroliths also are more resistant to ESWL, perhaps because they are not surrounded by fluid.[10] Cavitation bubble collapse may be a major mechanism of fragmentation in uroliths smaller than 2 mm. Because cavitation bubbles form in the fluid surrounding uroliths, impaction of small ureteroliths effectively prevents cavitation bubble formation and collapse. Ureteroliths that have been static for some time or that appear embedded in the ureteral wall on imaging studies may be impacted. One suggestion that a ureterolith is impacted is a duration at one location for 2 months or more.[28] With ureteroliths embedded in ureteral mucosa, fragmentation may appear adequate, but fragment movement does not occur. Minimal movement and minimal reverberation of SW within the stone also limit the fragmentation effect in the confined space of the ureter.[3,10] Factors limiting successful fragmentation in human patients and leading to increased diversion to ureteroscopic techniques have included larger stone size (greater than 10 to 12 mm), distal (pelvic) location,[29,30] degree of obstruction, and obesity.[30]

Finally, the availability of equipment and expertise is a major limiting factor, especially when emergency needs dictate prompt intervention. To accommodate timely referral and travel arrangements to one of the few existing centers for veterinary lithotripsy can be difficult. Because of the complexity of these cases and the many factors that must be considered in treatment planning, for the consulting urologist to recommend ESWL definitively or to provide a realistic prognosis before referral also are difficult. These practical concerns are exacerbated when considering the multiple ESWL treatments required in many patients. Some pet owners find the repeated evaluations, anesthetic episodes, hospitalizations, and additional costs unacceptable.

POTENTIAL MODIFICATIONS FOR FELINE EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY

Adjustments in treatment protocols may increase the safety and efficacy of lithotripsy treatment in cats. Modifications are likely to involve (1) adjustment of lithotriptor or lithotripsy dosage, (2) adjunct use of renoprotective agents, or (3) pharmacological enhancement of fragment movement.

Based on a growing body of research regarding SW-induced renal injury, modifications of the lithotripsy protocol can be recommended to limit injury. Limiting the number of SW applied and the rate (or frequency) of administration seems

most logical.[20-22,31,33] Most studies imply a 1500 to 2000 SW limit per treatment. However, additional costly treatment sessions may be necessary in veterinary patients if strict SW number limits are followed and treatments are abandoned at a fixed SW number. In one study of human patients, a slow lithotripsy rate (1/sec) was associated with a higher success rate and lower total SW dose when compared with a rate twice as fast; treatment time, naturally, was longer in the slow lithotripsy group.[33] Other investigators recommend a low energy level, high SW number protocol for pediatric and high-risk patients.

Recently, the role of cavitation bubbles in SW injury has come under study, and modifications to SW delivery by the lithotriptor designed to reduce cavitation are under review. In young pigs treated with a modified HM3 lithotriptor, reduced vascular injury and vasoconstrictive responses were attributed to suppression of cavitation.[32] Renal injury also is likely to vary, depending on the characteristics of the lithotriptor employed. Electromagnetic lithotriptors, such as the Storz Modulith SL20, create a much smaller renal lesion than electrohydraulic machines (such as the Dornier HM3), an advantage in treatment of smaller kidneys.[10] However, the severity of localized injury may be more dramatic with the electromagnetic units. Limiting energy applied can reduce injury.[34]

Renoprotection is directed at vascular or cellular components. Agents that prevent or mitigate vasoconstrictive responses associated with ESWL are studied most commonly, although transient vasoconstriction may actually prove protective against structural injury. Mannitol treatment has reduced the excretion of several indicators of renal damage after ESWL in human beings.[35] Cellular protection of the vessels and cells at the focal point may protect blood flow during ESWL; calcium-channel blockers and allopurinol have been shown to block renal functional changes.[36-40]

Agents that relax the ureter and allow freer passage of ureteral fragments also are intriguing adjuncts to EWSL in smaller patients. The pros and cons of glucagon, α-antagonists, and amitriptyline in the management of ureteroliths are highlighted in Chapters 41 and 43 in this text. In human beings, the selective α-adrenergic antagonist tamsulosin appears to have the most clinical promise for promotion of ureterolith passage.[41,42] Amitriptyline recently has been shown to blunt smooth muscle contraction in feline ureteral segments studied in vitro.[43]

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY FOR CYSTOUROLITHS

ESWL is not recommended widely for treatment of bladder stones, because mobile cystoliths are readily able to move out of the shock wave path within the bladder lumen. This movement limits the repeated shock wave effect on cystoliths and may result in larger fragments than desired. ESWL can, however, be used to reduce the size of cystoliths for either dissolution or hydropropulsion. Successful fragmentation of bladder stones using a water bath lithotriptor has been reported in a dog.[44] I* have successfully fragmented and then removed bladder stones via hydropropulsion in 12 of 16 dogs using the Dornier HM3. These dogs also were being treated with SWL for concurrent nephroliths. The dry Storz Modulith SL20 lithotriptor has been effective for fragmenting calcium oxalate and struvite bladder stones for sufficient passage in several female dogs and one cat (Figure 44-5), but ESWL fragmentation of cystoliths is less likely to be successful in male animals (especially male cats) because of the increased risk of urethral obstruction.

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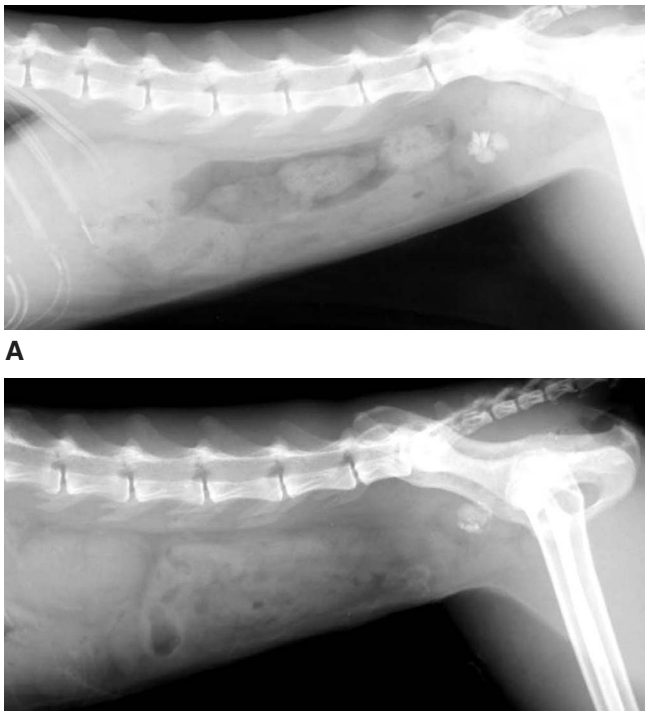

Figure 44-5. Feline cystoliths before and after extracorporeal shock wave lithotripsy. **A,** Lateral radiograph pre treatment. **B,** Radiographic appearance on day 2 after SWL.

CURRENT RECOMMENDATIONS REGARDING EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY IN CATS

At this time, the ideal candidate for ESWL is the cat with a single obstructive ureterolith separated by some distance from the kidney. Proximal ureteroliths and obstructive nephroliths of small size (less than 1 cm) also may be good candidates for ESWL, although the risk of renal injury increases. Owners of such cats must be prepared for multiple treatments and possible transient worsening of renal function or ureteral obstruction after ESWL. Surgical intervention or dialytic support may be necessary if these complications are severe. Adequate prehydration and fluid diuresis after treatment are essential. Ongoing medical management is critical to preventing recurrence. Potential modifications of lithotripsy protocols, including slow rate of delivery, low power regimens, and newer lithotriptors may minimize renal damage. Logical protective measures also may include pretreatment with mannitol or calcium-channel blockers.

ESWL also may be considered for female cats with multiple calcium oxalate or struvite cystoliths. However, cystotomy or intracorporeal laser lithotripsy are likely to be more efficient means of removal of symptomatic cystoliths and allow quantitative stone analysis.

INTRACORPOREAL SHOCK WAVE LITHOTRIPSY METHODS

Shock waves can be applied to uroliths by intracorporeal methods as well, including electrohydraulic (EHL) and laser methods. With EHL, an electrode is placed directly onto the urolith surface via a cystoscope. A spark generator is discharged at fairly high energy to fragment the stone. The stone usually is trapped with a stone basket for immobilization and to maintain the EHL probe in the lumen of the bladder.[3,46] With laser methods, the laser fiber also is directed through a cystoscope or ureteroscope to the urolith. The Ho:YAG laser uses the active medium of holmium, a rare earth element, and the YAG crystal to operate at a wavelength of 2100 nm, which creates photothermal energy that can be delivered through small, flexible fibers. The flexible laser fibers used for lithotripsy range from 200 to 365:m in size, and are applied via 5 Fr to 9 Fr instruments.[10] The lasers can be discharged in more confined spaces such as the urethra or ureter; however, they also must remain >0.5 mm away from mucosal surfaces. Halland, House, and George described successful obliteration of urethroliths in 3 goats and 2 pot-bellied pigs using a 200:m Ho:YAG fiber directed through a 8 Fr (2.7 mm) ureteroscopic instrument.[47] Davidson, Ritchey, Higbee, et al recently described the application of Ho:YAG laser energy to surgically implanted urethroliths placed at the base of the os penis of healthy dogs.[48] Ho:YAG laser lithotripsy also has been used to fragment spontaneous urethroliths and urocystoliths in male and female dogs via urethrocystoscopy. I* have successfully fragmented and removed calcium oxalate uroliths via transurethral cystoscopy in a female cat using the Ho:YAG laser; however, this technique is not possible in male cats because of size and anatomical limitations. In the future, a combination of open or laparoscopic approaches with laser technology may be possible for uroliths in male cats, similar to percutaneous procedures applied commonly in human beings.

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Chapter 45

PROTEINURIA

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Kidney diseases that lead to renal insufficiency and failure are extremely common in aging cats. Good epidemiological studies are lacking to determine the true prevalence of chronic renal insufficiency (CRI) and chronic renal failure (CRF), but estimates suggest that as many as one in three cats over the age of 12 may be affected.[1] The importance of proteinuria as a prognostic indicator and therapeutic target in feline chronic kidney disease only recently has been recognized. This chapter discusses the importance of assessment and classification of proteinuria in the feline patient with kidney disease, the mechanisms by which it may cause progressive renal injury, and the therapeutic approaches that can be used to treat significant proteinuria in cats.

DIAGNOSIS

Qualitative, or Screening, Tests for Proteinuria

The most common screening tests for proteinuria involve some form of colorimetric dipstick test. These tests are semiquantitative and depend on the ability of amino groups of proteins to combine with indicator dyes (e.g., tetrabromophenol blue), which then change color. The degree of color change depends on the number of free amino groups in the protein. Because albumin has more free amino groups than hemoglobin or globulins, the reagent pads usually are two to three times more sensitive to albumin in the urine than to other proteins. The individual tests vary in their lowest limits of detection, but usually produce a positive reaction only if protein is present at a concentration above 0.3 g/L. False-positive results are common in dipstick tests, particularly in alkaline urine, and positive results must be interpreted in light of urine specific gravity.[2]

An alternative screening test is the sulfosalicylic acid turbidimetric test. This involves addition of an equal volume of 3 per cent to 5 per cent sulfosalicylic acid to the urine sample and subjective assessment of the turbidity of the sample (0 to 4+). Highly alkaline urine may give false-negative results, but the likelihood of false-positive results is much lower with this screening test than the standard dipstick tests.

The final semiquantitative screening test that is widely available is the Early Renal Damage test (ERD, Heska Ltd., Fort Collins, CO). This is a sensitive immunological test that employs antibodies specific for feline albumin. Because of a lack of immunological cross-reactivity, tests that have been developed for use in other species cannot be used to detect feline albumin. The test kit provides a method of diluting the urine sample to a specific gravity of 1.010 to control for urine concentration and therefore urine volume. The cutoff between negative and weakly positive has been set for an albumin concentration of 1 mg/dL, a value some 30 times lower than most standard dipstick tests (although samples may be diluted several fold before testing). Therefore samples with the severity of proteinuria that traditionally has been considered clinically significant (i.e., those typically associated with primary glomerular disease) are likely to give readings in the high to very high positive range. The advantage of this test (and others like it) is its ability to detect low concentrations of protein that would not be detected by standard nonimmunological methodologies. The term microalbuminuria has been coined to describe the low concentration of urinary protein detected by these immunological methods.

Quantitative Tests for Proteinuria

The gold standard for assessing urinary protein loss is to collect all the urine passed by the animal for a 24-hour period, measure its volume and protein concentration accurately, and calculate the amount of protein lost (in milligrams of protein in urine per kilogram body weight) in the 24-hour period. The excretion of albumin over a 24-hour period can be measured in a similar manner. This technique is used only in the research setting, because facilities to allow 24-hour urine collection usually are not available in clinical practices.

Measurement of the urine protein to creatinine (UPC) ratio is used in veterinary practice as an alternative to measurement of 24-hour urine protein excretion. This method can be done on a single random (spot) urine sample. It is best performed after a period of confinement without access to a litter tray so

Table 45-1 | **Interpretation of Protein and Albumin Measurements in Feline Urine**

PARAMETER	CUT-OFF LEVELS	INTERPRETATION	COMMENTS
UPC	<0.2	Normal in human beings and cats*	Young healthy cats typically have UPCs of this magnitude[4,14]
	<0.4	Normal in aged cats	Based on data from 28 healthy cats aged 12.7 ± 2.5 years[15]
	0.4-2.0	Proteinuric (mild to moderate)	Could be indicative of glomerular or tubular dysfunction
	>2.0	Proteinuric (severe)	Likely to be the result of primary intrinsic glomerular disease
Albuminuria (mg/g)	<30	Normal in human beings	Probably suitable cut-point for microalbuminuria in cats; however, the reference range for albuminuria based on data from 28 healthy aged cats extended to 82 mg/g[15]
	30-300	Microalbuminuric	See text for discussion of possible significance
	>300	Macroalbuminuric	Use UPC to quantify further

*Intact male cats can have UPCs of up to 0.6.

that the volume of urine upon which it is based is as large as possible. Laboratories offering this test measure creatinine and protein by quantitative analyses, express the concentration of both analytes in grams per liter (g/L), and calculate the ratio of analyte concentrations. Such an approach has been shown to give results in cats that correlate with 24-hour urine protein excretion measured under research conditions.[3,4] Standard practice chemistry analyzers cannot be used to make measurements of urine protein and creatinine. These machines are calibrated for plasma in which the concentration of protein is 500 to 1000 times higher than in urine. Therefore cross-contamination of urine with protein from previously analyzed plasma samples is a significant problem. Furthermore, creatinine concentrations are 25 to 100 times higher in urine than in plasma, which makes it necessary to dilute urine samples considerably before the creatinine concentration falls within the working range of the machine. Suggested interpretations of UPC measurements in cats are presented in Table 45-1.

A similar approach can be adopted for quantifying albumin concentration in feline urine. Feline-specific ELISA assays have been produced and may be used to provide a quantitative evaluation of the albumin concentration in urine.[5] At present, we are aware of only one commercially available assay (Heska Corp., Fort Collins, CO). Traditionally, in human medicine, albumin has been quantified in milligrams per liter (mg/L) and creatinine in grams per liter (g/L), so the ratio has been expressed in units of mg albumin per g of creatinine. Few data published define microalbuminuria in cats. The cut-points used typically for human urine are 30 mg/g dividing between normal and microalbuminuric patients, and 300 mg/g dividing between microalbuminuria and grossly proteinuric (also termed macroalbuminuric). Preliminary observations made in our laboratory with use of a polyclonal sandwich ELISA test[5] suggest that similar cut-points may be appropriate for cats. However, if these definitions are accepted, some older, apparently healthy cats will be classified as microalbuminuric (see Table 45-1).

ETIOLOGY

The glomerular filter consists of the fenestrated endothelium of the glomerular capillary, the basement membrane, and the visceral epithelium. Of these three structures, the endothelium prevents passage of cells into the glomerular filter, the basement membrane provides structural stability of the filter, anchoring cells in the correct position, whereas the transmembrane proteins of the podocytes (visceral epithelium), which form the slit diaphragm, act as the primary charge and size selective filtration barrier.[6] Albumin appears in the ultrafiltrate at low concentrations, despite its presence in the plasma at high concentrations (about 0.5 mM). This is because, with a molecular weight of 69,000, it is close to the limit for filtration in terms of size. In addition, albumin is predominantly negatively charged and is repelled by the negatively charged proteins within the slit diaphragm. Nevertheless, recent data suggest a significant transglomerular flux of albumin so that more of this protein appears in the glomerular filtrate of normal kidneys than was once recognized.[7]

Small proteins of molecular weight less than 7,000 are unimpeded in passage across the glomerulus, but most of this filtered protein is removed from the glomerular filtrate as it passes through the proximal convoluted tubule. Protein is removed from filtrate by pinocytosis; tubular cells break down the reabsorbed protein into its constitutive amino acids. Albumin that passes across the glomerular filter is dealt with inefficiently by such a process, and therefore usually is the major urinary protein detected in normal healthy animals. For proteins with a molecular weight between 7,000 and 70,000, an increasing impediment to filtration occurs that is both size-dependent and charge-dependent. Loss of protein in the urine in normal healthy cats usually does not exceed 30 mg/kg/day.[3] In addition to small amounts of albumin, urine contains small amounts of protein secreted by the tubules (Tamm-Horsfall protein) and proteins that are derived from the lower urinary and genital tracts.

Classification of Proteinuria According to Site of Origin

The origin of protein appearing in the urine can be classified as prerenal, renal, or postrenal. *Prerenal proteinuria* implies that significantly increased concentrations of protein are being presented to the kidney in the plasma. If these proteins are of low molecular weight, they will be filtered and, if the concentration in the glomerular filtrate is sufficiently high, tubular reabsorptive processes will be overwhelmed. Examples of proteins that are filtered readily include immunoglobulin light chains, hemoglobin, and myoglobin. Some of these low molecular weight proteins are not detected by standard laboratory methods, which generally are more sensitive to albumin.

Postrenal proteinuria implies protein is added to the urine in the urinary tract after formation by the kidney (i.e., in the ureter, bladder, or urethra). Inflammation of the urinary tract,

resulting most commonly from bacterial infection, should be considered as a possible cause of proteinuria. Other causes include the presence of uroliths and tumors, both of which may cause inflammation directly or may be associated with secondary bacterial infection. In many, but not all cases, the cat will be showing signs of lower urinary tract disease, such as dysuria and pollakiuria. Microscopically, the urine sediment is likely to be active, with evidence of inflammatory cells and possibly bacteria. Samples of relatively dilute urine (urine specific gravity <1.030) should be submitted routinely for bacterial culture (even in the absence of lower urinary tract signs and microscopic evidence of inflammation) to rule out subclinical urinary tract infections before a postrenal cause for proteinuria is excluded categorically. However, in cats with CRF, positive urine cultures from samples with noninflammatory urine sediment are uncommon.

Renal proteinuria implies that defective renal function and/or inflammation of parenchymal kidney tissue is the cause of the proteinuria. Active, acute, renal parenchymal inflammation, associated with diseases such as pyelonephritis and acute tubular necrosis, may be suspected from the clinical history. Localization of the disease to the kidney may be possible based on physical examination findings (painful swollen kidneys on palpation, fever, renal failure), or resulting from the presence of tubular casts on urine microscopy. However, in many instances, a diagnosis of renal proteinuria is made by the exclusion of prerenal and postrenal forms of proteinuria. Renal proteinuria then may be characterized further as being of either glomerular or tubular origin.

Causes of Renal Proteinuria

Glomerular proteinuria can occur because of *primary glomerular pathology* leading to a defective filtration process. Examples of primary glomerular diseases include the following:

1. Glomerulopathies: Developmental abnormalities in the components of the basement membrane and slit diaphragm are well recognized in human patients and a number of canine breeds, but have not been reported in cats.
2. Glomerulonephritis with immune complex deposition in the glomerulus: Idiopathic membranoproliferative glomerulonephritis has been reported in cats, but represents a small proportion of the kidney diseases seen in veterinary practice.[8,9]
3. Amyloid deposition in the glomerulus: Renal amyloidosis has been reported in cats, most often in Abyssinians. The renal medulla is most affected, and as a consequence these cats are not invariably proteinuric.[10]

In primary glomerular diseases, the magnitude of proteinuria tends to be high (UPCs >2.0, and often above 5 to 10), a feature that may be helpful in distinguishing these diseases from other causes of renal proteinuria. Very high levels of proteinuria (UPC >10) may be associated with clinical signs of the nephrotic syndrome (peripheral edema or ascites). Cats with severe proteinuria are not always azotemic when their kidney disease is diagnosed. Many proteinuric cats become azotemic over time, because persistent proteinuria of this severity leads undoubtedly to progressive renal injury, as discussed in the next section of this chapter. However, in the authors' experience, nonazotemic cats that present with signs of the nephrotic syndrome may respond favorably to treatment, at least in the short to medium term.

Low-level proteinuria (UPCs 0.4 to 2.0) and microalbuminuria also may be caused by increased protein flux across the glomerulus in the absence of classical primary glomerular diseases such as those described above. *Increased transglomerular flux* of proteins (particularly albumin) may occur because of the following:

1. Glomerular capillary hypertension: Increased glomerular capillary pressure may develop as a maladaptive response to the loss of functioning nephrons in patients with chronic progressive renal disease.
2. Endothelial cell dysfunction: Cellular dysfunction has been associated with a number of disease states, including chronic kidney disease, possibly as a result of increased oxidative stress.

A further potential cause of low-level proteinuria (UPCs 0.4 to 2.0) is *defective tubular reabsorption of the filtered protein*. This may occur as one feature of a more generalized tubular defect, characterized by normoglycemic glucosuria or abnormal electrolyte secretion, or more often as a consequence of a decrease in the number of functional tubules in patients with chronic progressive renal disease. Probably in many patients, the renal defects resulting in mild proteinuria are a combination of increased transglomerular flux and decreased tubular reabsorption.

ROLE OF PROTEINURIA IN THE PROGRESSION OF RENAL DISEASE

Historically, only moderate-to-severe proteinuria (typically with UPC >1.0) has been considered of clinical significance in veterinary practice. Certainly only protein loss of this magnitude or greater is likely to result in systemic hypoalbuminemia and other features of the nephrotic syndrome. However, most cats with azotemic chronic progressive renal disease have either normal levels of protein in their urine, are microalbuminuric, or have mild proteinuria (UPCs >0.4 but <1.0). Although moderate-to-severe proteinuria has been shown to predict a more rapidly progressive decline in renal function in a number of species, including human beings[11] and dogs,[12] the significance of mild proteinuria, such as is typically present in cats with CRF, is less well documented. The main focus of this chapter is on the significance of urinary protein in the azotemic cat with chronic kidney disease. Two primary, interrelated questions must be addressed: Is mild proteinuria of clinical significance in cats (i.e., is proteinuria associated with a more rapid decline in renal function) and, if so, is the proteinuria actually damaging to the kidney or is it simply a marker for a more rapidly progressive type of renal injury?

Glomerular Capillary Hypertension

In rodent models of chronic kidney disease, after loss of a critical amount of renal mass, local changes within the kidney result in hyperfiltration of the remaining functioning nephrons and low-level proteinuria. The hyperfiltration is driven by glomerular capillary hypertension, which in turn is caused, at least in part, by local activation of the renin-angiotensin system

(RAS). This is due to the increased local concentration of angiotensin II, which causes selective constriction of the efferent arteriole. In addition, angiotensin II stimulates nephron hypertrophy. Ultimately, over time, these adaptive changes are detrimental (*maladaptive*) and are thought to lead to interstitial fibrosis and inflammation resulting in further nephron loss, even in the absence of any extrinsic factors that damage the kidney (the so-called "intact nephron hypothesis"[13]).

Evidence that glomerular capillary hypertension occurs in the feline kidney also has been documented using a remnant kidney model.[14] Surgical reduction in renal mass (three-quarters nephrectomy) caused an approximately 10 per cent rise in glomerular capillary pressure, measured by micropuncture techniques. In these six cats, development of glomerular hypertension was associated with an increase in protein excretion. Before renal injury, the cats had a mean UPC of 0.07 ± 0.01; after subtotal nephrectomy, the mean UPC increased to 0.31 ± 0.06.[14] Chronic maintenance of this model is associated with development of interstitial fibrosis, moderate inflammatory infiltrate of the interstitium, and glomerulosclerosis, as is seen in the rodent model described above.

What evidence do we have that similar changes occur in cats with spontaneous, naturally occurring, renal disease? In a cross-sectional epidemiological study of 94 cats at initial diagnosis of their chronic kidney disease and 42 nonazotemic aged cats,[15] urine protein excretion was measured and multivariate logistic regression used to determine risk factors for proteinuria (Figure 45-1). Significant risk factors included initial plasma creatinine concentration and increased systolic blood pressure.[15] Age, urine specific gravity, and gender were not associated significantly with the magnitude of proteinuria. Additional, longitudinal studies have demonstrated that proteinuria, as assessed by the UPC ratio, worsens in cats when their renal function deteriorates.[16]

These observations provide circumstantial evidence to support the hypothesis that cats with naturally occurring chronic kidney disease develop proteinuria as a result of development of glomerular hypertension, because hyperfiltration would be expected to be more severe in cats with fewer functioning nephrons and consequently more marked elevation of plasma creatinine concentration. However, interpretation of a changing UPC in the face of loss of functioning nephrons is complex, because the reduced number of nephrons filtering the blood offsets the tendency for protein loss to increase.

Systolic blood pressure also was linked to the severity of proteinuria in these cats.[15] The increased proteinuria in hypertensive cats could be due to an inability of the failing kidney to autoregulate renal blood flow appropriately, with resultant transmission of the elevated systemic blood pressure to the glomerulus. An alternative explanation is that proteinuric renal diseases are more likely to cause systemic hypertension.

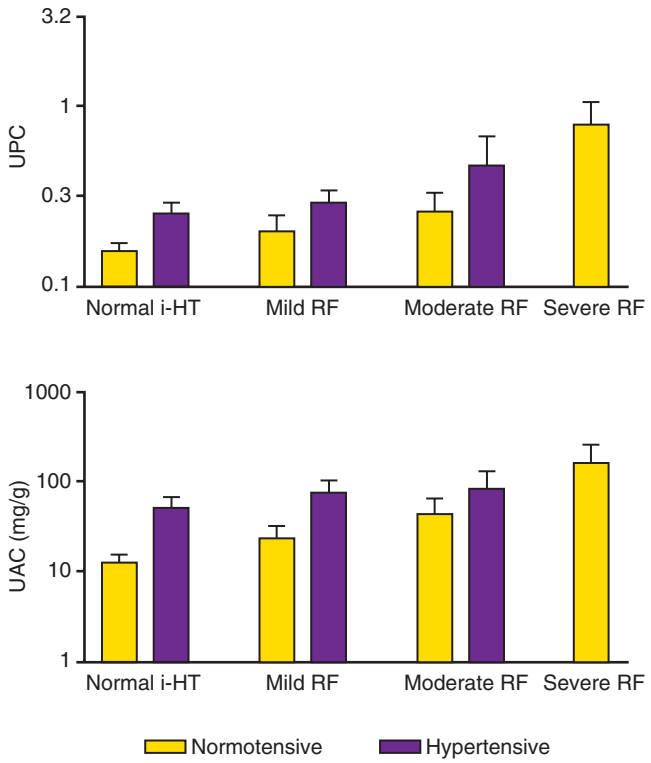

Figure 45-1. The relationship of proteinuria to severity of azotemia in normotensive and hypertensive cats. Bars represent mean ± SEM (note log scale) for cats with normal plasma creatinine concentration (normal, n = 28), normal plasma creatinine and thyroxine concentration but elevated systolic blood pressure (idiopathic hypertension; i-HT, n = 14) or renal failure (RF). Renal failure was categorized into mild (2.0-2.84 mg/dL), moderate (2.84-4.55 mg/dL), or severe (>4.55 mg/dL) based on plasma creatinine concentration. Data from normotensive (n = 32, 21, and 13 in mild, moderate, and severe categories, respectively) and hypertensive (n = 22 and 5 in mild and moderate categories) cats are plotted separately for comparison. Cats were considered hypertensive if systolic blood pressure was greater than 175 mm Hg on more than one occasion, or if it was greater than 175 mm Hg on a single visit and hypertensive retinopathy/choroidopathy was present.

Proteinuria and Survival Time of Cats with Chronic Renal Disease

The cats included in the cross-sectional epidemiological study referred to above also were enrolled in a longitudinal study of survival time.[17] A total of 117 cats were included, with 19 of the original cats being excluded because the owners did not know their age (n = 10) or because no follow-up information was available (n = 9). Cox's proportional hazards model was used to determine the influence of age, gender, plasma creatinine concentration, systolic arterial blood pressure, and UPC ratio on survival time. In this study, log UPC as a continuous variable proved to be associated significantly and independently with survival as were age and plasma creatinine concentration. No association was found between gender or systolic blood pressure and survival. For illustrative purposes, the survival curves for cats with variable magnitude of proteinuria (divided into quartiles), and adjusted for any influence of creatinine concentration and age, are depicted in Figure 45-2.

The results of these studies demonstrate that proteinuria is associated with shortened survival times in cats with naturally occurring kidney disease. However, because only about half of the cats suffering from chronic kidney disease in our clinic population die or are euthanized because of progressive renal failure or an acute uremic crisis, rapid decline in renal function may not be the sole reason for the decreased survival times in cats with proteinuria. In human beings with renal disease, proteinuria has been found to predict morbidity and mortality resulting from a number of diseases in addition to progressive renal failure. In particular, proteinuria is associated with an

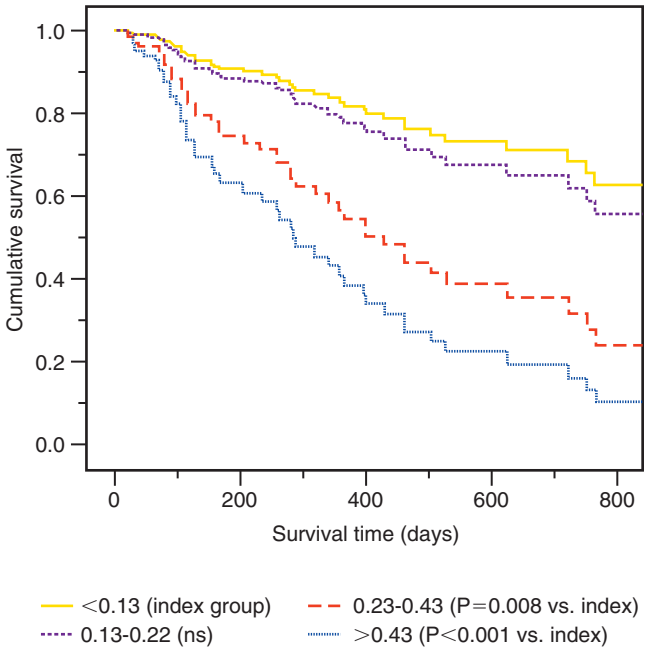

Figure 45-2. Influence of proteinuria on the survival times of cats. The data displayed are multivariate cox survival analysis for 117 cats (38 nonazotemic and 79 azotemic) segregated into quartiles according to the magnitude of their proteinuria. Other covariates found to be significantly predictive of survival time; plasma creatinine concentration ($P < 0.001$) and age ($P = 0.025$) are controlled for in the graph that is displayed (covariate means are 2.65 mg/dL for the plasma creatinine concentration and 13.3 years for the age). Proteinuria was associated significantly with a shortened survival time ($P < 0.001$), with cats from both the third and the fourth quartile of proteinuria having significantly shortened survival times, compared with cats in the first quartile.

increased risk of cardiovascular events,[18] which perhaps reflect a state of generalized endothelial dysfunction.[19]

One conclusion from these studies is that interventions designed to reduce urinary protein excretion would slow progressive renal injury and therefore improve survival in cats with chronic kidney disease. This conclusion assumes that protein in the urine in these animals is damaging to the remaining functional nephrons and leads to progressive renal injury. Another interpretation of these findings, however, is that the appearance of protein in the urine is merely a marker that progressive renal injury is occurring.[20] In this case, although renoprotective interventions may be expected to reduce protein excretion because they slow progressive renal injury, reducing urine protein excretion *per se* does not necessarily prove to be renoprotective.

Mechanisms for Progressive Renal Injury Resulting from Proteinuria

In vitro studies have shown that exposure of proximal tubular cells grown in cell culture to albumin and transferrin in concentrations that overwhelm the ability of these cells to digest the proteins within their lysosomes leads to activation of nuclear factor κB (NF-κB). This nuclear factor in turn triggers the expression of genes in these cells and causes them to secrete mediators from their basolateral cell surfaces (i.e., towards the interstitium).[21] These mediators include endothelin-1 (ET-1), monocyte chemotractant protein-1 (MCP-1), and the immunoregulatory cytokine regulated on activation, normal T expressed and secreted (RANTES). Expression and secretion of these proteins can be demonstrated in vivo in animal models of proteinuric renal disease.[22] Interventions that reduce proteinuria in these models also reduce the expression of these and other cytokines involved in the progressive interstitial fibrosis. These molecular details may explain why proteinuria is an independent risk factor for progression of kidney disease in human medicine, and why drugs such as angiotensin-converting enzyme (ACE) inhibitors slow progression successfully in proteinuric kidney diseases, independent of their effects on systemic arterial blood pressure.

Significance of Proteinuria in Nonazotemic Animals

With the advent of bench-top diagnostic tests for microalbuminuria, interest has increased in the significance of mild proteinuria in nonazotemic animals. Tests for microalbuminuria have been proposed as a marker of subclinical renal injury, more sensitive than the onset of azotemia, which typically does not develop until at least three quarters of nephrons have been lost. In human beings and dogs, microalbuminuria has been shown to precede development of renal failure, at least in populations at high risk for developing glomerular disease.[23,24] No similar studies have been performed in cats. However, microalbuminuria and mild proteinuria were found to be predictive of all-cause mortality in a population of nonazotemic, apparently healthy cats.[25] This study involved 59 cats, 15 of which died during the follow-up period (median follow-up time of 357 days in the cats that died and 507 days in the survivors). The survivors had significantly lower UPC ratios when compared with the nonsurvivors (median value 0.16 versus 0.3). Because this study included all-cause mortality, the results cannot be interpreted to answer the question as to whether microalbuminuria is a marker for subclinical renal disease, is predictive for a progressive decline of renal function, or is a marker for some other disease state. Prospective studies are warranted to address this question.

Many systemic disease states have been associated with microalbuminuria, including a variety of chronic inflammatory diseases and neoplastic conditions. In a study of 611 apparently healthy cats, the prevalence of microalbuminuria was 13.7 per cent.* By comparison, the prevalence of microalbuminuria in cats with a known medical problem was 42.9 per cent. Interestingly, although the prevalence of microalbuminuria increased with age in both groups, this increase was much more marked in the apparently healthy cats, perhaps because of an increased prevalence of subclinical renal disease in the elderly cats. However, interpretation of the significance of a positive test for microalbuminuria is difficult in any individual cat. Indeed, even if microalbuminuria is a marker for incipient renal disease, many of the other diseases linked with it likely will lead to the death of the cat before renal disease is of any clinical consequence.

One important disease that may cause microalbuminuria and mild proteinuria in cats is hyperthyroidism. The hyperthyroid state leads to glomerular hyperfiltration and probably glomerular capillary hypertension because of inappropriate activation

* http://www.heska.com/erdscreen/erd_datacat.asp.

of the renin-angiotensin system. In one study, approximately one half of untreated, nonazotemic, hyperthyroid cats had UPCs on initial diagnosis of >0.5 (i.e., were mildly proteinuric).[26] Management of the hyperthyroid state resulted in a rapid reduction in UPC ratio in the majority of the cats, which suggests that the renal hemodynamic effects of thyroid hormones caused the proteinuria.[26] This finding lends credence to the proposition that if hyperthyroidism is left untreated, it is damaging to cats' kidneys. However, the degree of proteinuria at diagnosis was not predictive of the occurrence of azotemia once the cats were stabilized in a euthyroid state.

TREATMENT

Cats with Chronic Renal Disease

If proteinuria proves directly injurious to the feline kidney, therapeutic strategies to lower glomerular capillary pressure and reduce proteinuria in cats with CRF should slow progressive renal injury (including interstitial fibrosis) and subsequently improve survival. Benazepril is an ACE inhibitor that is authorized for this indication in Europe at a dose rate of 0.5 to 1 mg/kg PO q24h. Benazepril has been shown to reduce glomerular capillary pressure in cats with experimentally reduced renal mass without compromising single nephron glomerular filtration rate.[27] The antiproteinuric effect of this drug also has been demonstrated in clinical cases of naturally occurring feline CRF.[28] However, the effect of benazepril on survival was not statistically significant, except in a very small subgroup of cats with pretreatment UPCs greater than 1.[28] Reducing proteinuria protected against development of interstitial and glomerular lesions in dogs with surgically reduced renal mass treated with enalapril (0.5 mg/kg PO q12h[29]). On balance, this evidence suggests that preventing or reducing proteinuria should be a treatment goal for all feline patients with CRF; however, the benefits of ACE inhibitor therapy are likely to be greatest in cats that are most proteinuric. Benefits also are only likely to be manifest in cats that are expected to survive for a reasonable length of time after initiating the treatment. Renal function in cats that are severely azotemic and likely to live for only a few days or weeks actually may be affected adversely by the drop in glomerular capillary pressure associated with ACE inhibition.

Several questions remain pertinent regarding initiation of ACE inhibitor treatment. Should ACE inhibitors be prescribed for all cats in renal failure? If not, at what level of proteinuria should treatment with ACE inhibitors commence? What should target post-treatment urinary protein concentration be? These questions will not be answered until further prospective clinical trials have been undertaken to ascertain the benefits of reducing protein excretion to different target levels. Currently, based on the epidemiological data discussed above, the authors recommend treating all cats with UPCs greater than 0.4 and aiming for a post-treatment UPC persistently lower than 0.4.

Cats with Chronic Renal Disease and Hypertension

An additional consideration in selection of therapy for proteinuria in cats with chronic kidney disease is control of systemic arterial blood pressure. Systemic hypertension is a risk factor for proteinuria; effective control of hypertension is important in limiting glomerular capillary hypertension. ACE inhibitors, although effective at lowering pressure within the glomerular capillaries, are not very effective at lowering systemic arterial blood pressure. Therefore, in a hypertensive cat, use of the calcium-channel blocker amlodipine would be the treatment of choice because this is the only agent demonstrated to consistently reduce blood pressure sufficiently to prevent development of hypertensive ocular lesions.[30] However, treatment with calcium-channel blockers has the disadvantage that it dilates the afferent renal arteriole but not the efferent arteriole, which nullifies any protective autoregulatory response and exposes the glomerulus to systemic blood pressure. This is only likely to be of real concern if control of systemic blood pressure is inadequate (i.e., systolic blood pressure remains above 160 mm Hg).[31]

A practical approach therefore in hypertensive cats is to manage systemic hypertension with amlodipine initially. Once blood pressure is well controlled, protein excretion should be reevaluated. If the UPC at this stage is greater than 0.4, addition of an ACE inhibitor to the treatment regimen should be considered. Although no objective data are available to demonstrate that combined therapy with amlodipine and benazepril in cats alters survival time or delays the progression of renal disease, short-term treatment with this combination of drugs has been described and appears to be well tolerated.[32] Adequate control of hypertension in cats with CRF should be documented by consistent indirect systolic blood pressures below 160 mm Hg. In human medicine, post-treatment blood pressure targets vary with the clinical condition of the patient, and targets are lower in patients with more severe proteinuria.[11] To give similar recommendations for feline practice is not possible at the present time.

Feeding a diet with a relatively reduced protein and phosphate content is a cornerstone in the management of CRF in cats. Although the benefits of ACE inhibitors are largely unproven and likely to be small in terms of increases in survival time unless patients are grossly proteinuric, survival time of cats that eat phosphate-restricted, "renal care" diets is much longer than of the cats that do not.[33] The primary benefits of this dietary strategy are amelioration of renal secondary hyperparathyroidism and attenuation of the severity of uremia. Additionally, protein ingestion contributes to glomerular hypertension in dogs and people with renal insufficiency; glomerular hypertension may exacerbate proteinuria. Although dietary restriction of protein appears to delay progression of renal disease in laboratory rats, the benefit of protein restriction alone has not been documented consistently in other species. Protein restriction does appear to limit urinary protein loss in dogs and human beings with glomerulonephritis, and is recommended in the treatment of patients that are severely proteinuric (even if they are nonazotemic). Anecdotally, reduction in dietary protein content also has been helpful in the management of cats with nephrotic syndrome.

Other potential therapeutic strategies to lower urinary protein excretion include the following:

- *Eicosapentaenoic acid supplementation*: In studies of dogs with the remnant kidney model of CRF, dietary supplementation with omega-3 polyunsaturated fatty acids (PUFA) reduced proteinuria and slowed renal disease progression,[34] whereas supplementation with omega-6 polyunsaturated fatty acids increased proteinuria and enhanced progression.[35] The authors are

not aware of any published data on the benefit of n3-PUFAs in cats with either naturally occurring or experimentally induced kidney disease.

- *Endothelin receptor antagonists*: The role of endothelin-1 in progressive renal injury has been the focus for intensive study. A recent study suggests the selective endothelin receptor antagonists have the greatest promise as renoprotective agents in human patients.[36] No published data are available on the use of these drugs in feline clinical patients.
- *Calcium-channel receptor antagonists* with relative selectivity for the efferent arteriole: Novel calcium-channel antagonists (manidipine, nilvadipine, benidipine, and efonidipine) potently dilate afferent and efferent arterioles.[37] Vasodilator action on efferent arterioles is mediated by blockade of T-type calcium channels and the inhibition of the intracellular calcium release mechanism. In a variety of experimental rodent models of hypertension and renal injury, these novel calcium-channel antagonists seem to be as effective as enalapril in their antiproteinuric effects.[37] Efonidipine has undergone clinical trials in human patients. At the present time, no information exists pertaining to use of these agents in feline patients, but if they prove beneficial in other species, they may be investigated in the future.

Nonazotemic Cats

No specific, evidence-based recommendations currently can be made for the treatment of cats with mild proteinuria or microalbuminuria that are not azotemic. If, in the future, mild proteinuria or microalbuminuria can be shown definitively to result from renal damage, and if any of the interventions described above can be proven clearly to be beneficial, then their use could be extended logically to nonazotemic patients. At the present time, the authors consider using these treatments (dietary protein reduction and ACE inhibition) in nonazotemic cats with moderate-to-marked proteinuria (UPC >1.0). In nonazotemic cats that are persistently microalbuminuric, or mildly proteinuric (UPC <1.0), we would confine our efforts to ruling out a prerenal or postrenal cause for the proteinuria and to searching for any associated underlying disease.

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Chapter 46

Dietary Considerations for Calcium Oxalate Urolithiasis

Claudia A. Kirk and Joseph W. Bartges

Cats have experienced a dramatic increase in the prevalence of calcium oxalate uroliths since the mid 1980s. Calcium oxalate is the most common mineral component found in feline uroliths, although the mineral component of urethral matrix-crystalline plugs is predominantly struvite.[1] Data from the Minnesota Urolith Center indicate calcium oxalate uroliths represented less than 5 per cent of feline urolith submissions before 1987 and rose to 55 per cent of the submissions in 1999 (Figure 46-1).[2] Although the etiology of feline urolithiasis is multifactorial, strong evidence suggests that nutritional factors influence disease expression and prevention significantly.

PATHOGENESIS OF STONE FORMATION

Calcium oxalate urolithiasis is not a specific disease, but results from underlying disorders that promote precipitation of calcium oxalate in urine. Epidemiological studies have identified numerous genetic, environmental, and nutritional factors associated with development of calcium oxalate uroliths. Epidemiological associations of risk do not represent simple cause-and-effect scenarios. The identified risk factors may or may not be causal and controlled studies are needed to confirm a direct link. An example is the association of feline hairball remedies with calcium oxalate urolith occurrence. Instead of hairball remedies causing uroliths, a more likely scenario is that hairball preventatives are used frequently in Persian cats, which are a breed at risk. Understanding the pathogenesis of calcium oxalate urolith formation aids in the interpretation of epidemiological findings and directs interventions to reduce the overall risk.

Mechanisms of Urolith Formation

Overview

Urolith formation, dissolution, and prevention involve complex physiochemical processes. Major factors include (1) urine supersaturation resulting in crystal formation (nucleation), (2) the effect of inhibitors of mineral nucleation, crystal aggregation, and crystal growth, (3) crystalloid complexors, (4) effects of promoters of crystal aggregation and growth, (5) effects of noncrystalline matrix, and (6) sufficient urine retention time or slowed transit for the process to occur (Figure 46-2).[3,4]

Concept of Urine Saturation

The most important driving force behind urolith formation is supersaturation of urine with calculogenic substances.[3] Additionally, urine contains ions and proteins that interact and/or complex with calcium and oxalic acid to allow them to remain in solution. This explains why calcium and oxalic acid in urine normally do not precipitate to form calcium oxalate crystals. Compared with water, urine normally is supersaturated with respect to calcium and oxalic acid. However, energy is required to maintain this state of calcium and oxalic acid solubility, and the maintenance of calcium and oxalic acid in solution remains tenuous. Therefore urine is described as being metastable, which implies varying degrees of instability with respect to the potential for calcium oxalate crystals to form (Figure 46-3). In this metastable state, new calcium oxalate crystals do not precipitate spontaneously, but if present already, crystals can be maintained and even grow in size. If the concentration of calcium and oxalic acid is increased, a threshold eventually is reached at which urine cannot hold more calcium and oxalic acid in solution. The urine concentration at which this occurs is the *thermodynamic formation product* of calcium oxalate. Above the thermodynamic formation product, urine is *oversaturated* and unstable with respect to calcium and oxalic acid. Therefore calcium oxalate crystals precipitate spontaneously, grow in size, and aggregate. In reality, most calcium oxalate stones form within the metastable region rather than in the region of oversaturation. As saturation increases, protective factors are reduced, or promoters increase, the urine stability

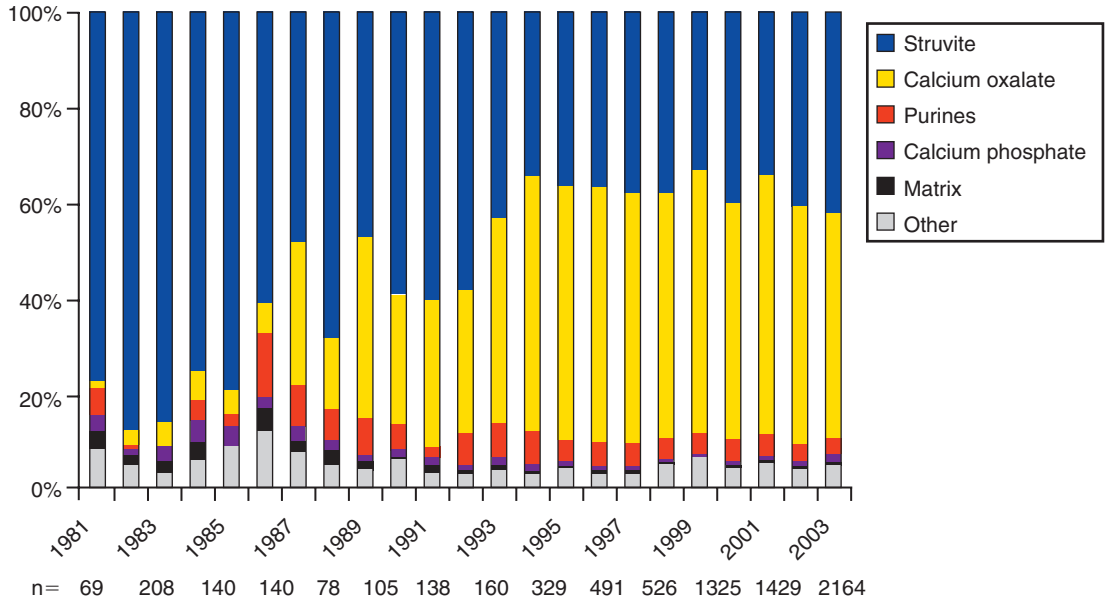

Figure 46-1. Changing trends in mineral composition of feline uroliths submitted to the Minnesota Urolith Center. (Data courtesy University of Minnesota Urolith Center.)

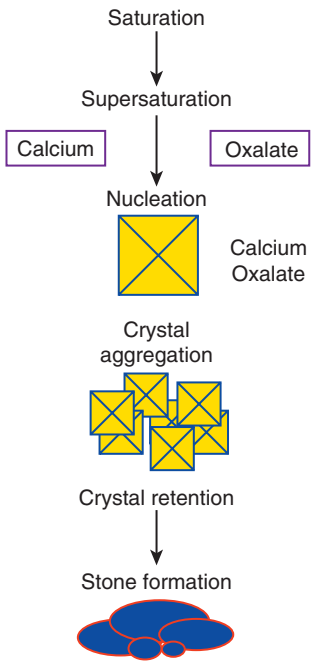

Figure 46-2. Sequence of events leading to calcium oxalate urolith formation.

declines, and crystallization occurs. (See Volume 4, Chapter 46, for an expanded description of urine saturation principles.)

For uroliths that do not dissolve in physiological solutions (such as calcium oxalate), nutritional therapy is designed to prevent further urolith formation or recurrence. The goal is to promote a state of urine undersaturation or reduced saturation to the point of least metastability (see Figure 46-3).

Calcium Oxalate Crystallization and Urolith Formation

Overview

Calcium oxalate urolith formation occurs when urine is oversaturated with calcium and oxalate.[3,4] Once initiation of urolith formation has occurred, the nidus must be retained within the urinary tract, and conditions must favor continued precipitation of minerals to promote growth of uroliths. Alterations in balance between urine concentrations of calculogenic substances (calcium and oxalic acid) and crystallization inhibitors (including citrate, phosphorus, magnesium, sodium, and/or potassium) have been associated with initiation and growth of calcium oxalate uroliths.[3-5] In addition to these alterations in activities of ions, large molecular weight proteins occurring in urine, such as nephrocalcin, uropontin, and Tamm-Horsfall mucoprotein, have an influence on calcium oxalate formation.[6] Currently, we have a limited understanding of the role of these macromolecular and ionic inhibitors of calcium oxalate formation in cats.

Etiologic Risk Factors

Certain metabolic factors are known to increase the risk of calcium oxalate urolith formation in several species, including cats. Medical and nutritional strategies for stone prevention have focused on amelioration of these factors.

HYPERCALCEMIA. Hypercalcemia is associated with increased risk of calcium oxalate urolith formation. Hypercalcemia has been observed in 35 per cent of cats with calcium oxalate uroliths.[1] Conversely, in 20 cats with idiopathic hypercalcemia, uroliths developed in 35 per cent of the affected cats.[7] When severe, hypercalcemia results in increased fractional excretion of calcium and hypercalciuria (see Chapter 17).

HYPERCALCIURIA. Hypercalciuria is a significant risk factor but not necessarily the cause of calcium oxalate urolith

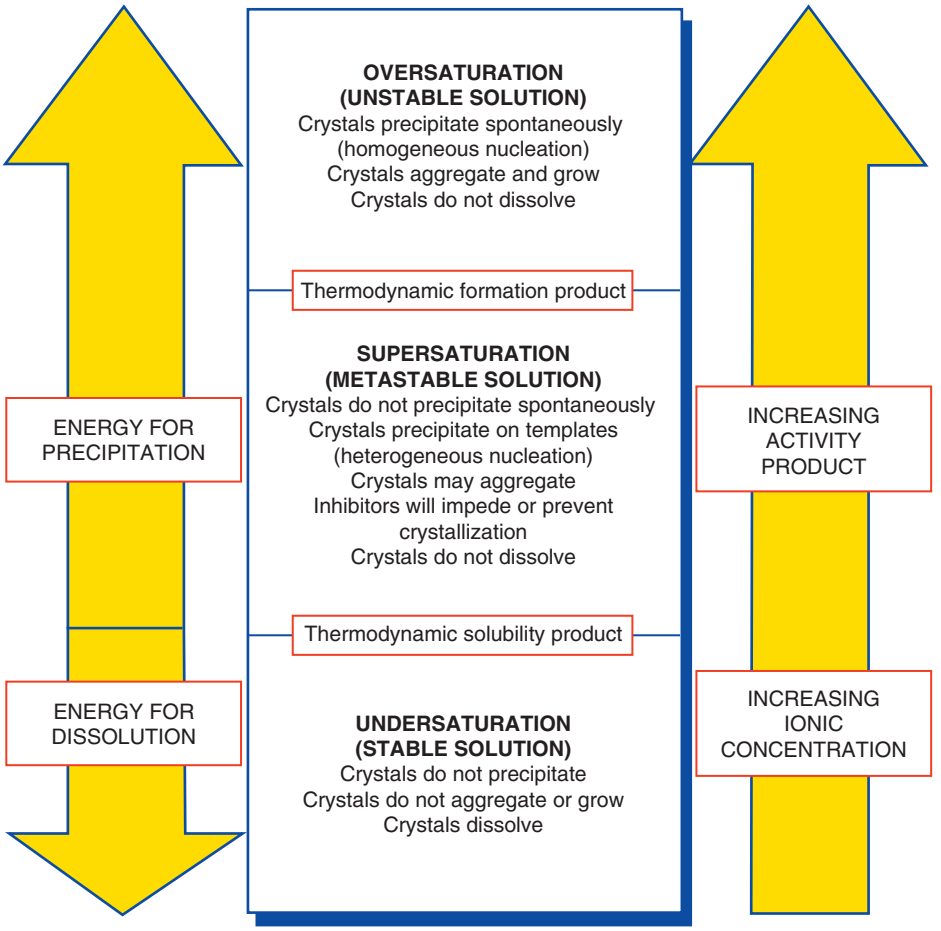

Figure 46-3. States of saturation.

formation in human beings, dogs, and cats.[8] Calcium homeostasis is achieved through actions of parathyroid hormone (PTH) and 1,25-dihydroxycholecalciferol (1,25-vitamin D) on bone, intestines, and kidneys (see Chapter 17). When serum ionized calcium concentration decreases, PTH and 1,25-vitamin D activities increase, which results in mobilization of calcium from bone, increased absorption of calcium from intestine, and increased reabsorption of calcium by renal tubules. Factors that alter the activity of these two hormones at any level alter calcium absorption, metabolism, and excretion. Hypercalciuria can result from excessive intestinal absorption of calcium (gastrointestinal hyperabsorption), impaired renal reabsorption of calcium (renal leak), and/or excessive skeletal mobilization of calcium (resorptive).[3] In miniature Schnauzers, gastrointestinal hyperabsorption appears to occur most commonly, although renal leak hypercalciuria also has been observed.[9] Hypercalciuria in the absence of hypercalcemia has not been well defined in cats with calcium oxalate uroliths but is thought to occur.

ACIDEMIA. Metabolic acidosis promotes hypercalciuria by promoting bone turnover (release of calcium with buffers from bone), which increases serum ionized calcium concentration and results in increased urinary calcium excretion and decreased renal tubular reabsorption of calcium. Consumption by cats of diets supplemented with the urinary acidifier ammonium chloride has been associated with increased urinary calcium excretion.[10] Additionally, consumption of diets high in animal proteins by human beings results in metabolic acid production and increased urinary calcium excretion.

ACIDURIA. Significant aciduria (urine pH less than 6.2) may represent a risk factor for calcium oxalate formation because of the associated acidemia and hypercalciuria. In addition, acidic urine alters the function and concentration of some crystallization inhibitors. Low urine pH decreases urinary citrate concentration by increasing renal proximal tubular citrate reabsorption. Acidic urine also is known to impair the function of macromolecular protein inhibitors.[8]

INHIBITORS. Inhibitors of crystallization such as citrate, magnesium, and pyrophosphate form soluble salts with calcium or oxalic acid and thereby reduce the availability of calcium or oxalic acid for precipitation. Other inhibitors, such as Tamm-Horsfall glycoprotein and nephrocalcin, interfere with the ability of calcium and oxalic acid to combine, which thereby minimizes crystal formation, aggregation, and growth.

HYPEROXALURIA. Oxalic acid is a metabolic end-product of ascorbic acid (vitamin C) and several amino acids, such as glycine and serine, derived from dietary sources. Oxalic acid forms soluble salts with sodium and potassium ions but a

relatively insoluble salt with calcium ions. Therefore any increased urinary concentration of oxalic acid may promote calcium oxalate formation. Increased dietary intake of oxalate and vitamin B_6 deficiency are two known factors that increase urinary oxalate. Hyperoxaluria has been observed experimentally in kittens consuming vitamin B_6-deficient diets,[11] but has not been associated with naturally occurring calcium oxalate urolith formation.

Genetic anomalies also may increase urine oxalic acid concentration. Hyperoxaluria has been recognized in a group of related cats with reduced quantities of hepatic D-glycerate dehydrogenase, an enzyme involved in metabolism of oxalic acid precursors (primary hyperoxaluria type II).[12] Hyperoxaluria also has been associated with defective peroxisomal alanine/glyoxylate aminotransferase activity (primary hyperoxaluria type I) and intestinal disease (enteric hyperoxaluria) in human beings, disorders that have not been investigated in the feline population.

URINE CONCENTRATION. Increasing urine concentration results in increased calcium and oxalic acid saturation and an increased risk for urolith formation. In fact, dilution of urine concentration with a substantial increase in water intake is the mainstay of calcium oxalate prevention in human beings. Cats can achieve urine specific gravities in excess of 1.065, which indicates a marked ability to produce concentrated urine. Many cats affected with calcium oxalate uroliths have a urine specific gravity greater than 1.040, unless some impairment occurs to renal function or concentrating ability.[8]

CALCIUM OXALATE CRYSTALLURIA. Detection of calcium oxalate crystals in urine sediment indicates that urine is supersaturated with calcium oxalate. Persistent crystalluria reflects an increased risk for calcium oxalate urolith formation. However, calcium oxalate crystalluria is observed in less than 50 per cent of feline cases at time of diagnosis of urolithiasis.[8]

EPIDEMIOLOGY

Epidemiological risk factors for calcium oxalate urolith formation include breed, gender, age, environmental factors, and diet. Because of the complexity of urolith formation, no one factor is likely to be causal. Medical and nutritional recommendations are designed to reduce the overall risk of urolith formation by addressing all factors that can be altered safely.

Nonnutritional Factors

Breed

Calcium oxalate urolith formation occurs in many breeds of cats. Most stones are submitted from domestic shorthair cats because of breed prevalence. However, Himalayan and Persian cats appear to be at greatest risk, along with ragdoll, British and exotic shorthair, Havana brown, and Scottish fold breeds.[13-15]

Gender

In dogs and human beings, males are affected more commonly with calcium oxalate uroliths than females. This same trend is evident in the feline population, although the disparity between genders is far less obvious. The male-to-female ratio of calcium urolith formation is 3.5:1.0 in human beings,[16] 2.7:1.0 in dogs,[17] and 1.4:1.0 in cats.[15] The overall risk ratio for calcium oxalate urolithiasis in males is 1.5 times the risk in females.[15] Regardless of gender, neutering is associated with a sevenfold increase in calcium oxalate uroliths.[15]

Age

The risk of struvite or calcium oxalate formation is inversely related to age in cats. This observation may be related to changes in urine composition and calcium oxalate saturation with age. Young cats have higher struvite and lower calcium oxalate urine saturation compared with older cats in which low struvite and higher calcium oxalate urine saturation has been observed.[18] Although cats of any age may form calcium oxalate uroliths, cats at greatest risk for calcium oxalate urolithiasis are between 7 and 10 years old, with the mean age at diagnosis of 7.5 years.[15]

Environmental Factors

Environmental factors have not been evaluated extensively in cats. Cats housed indoors exclusively experience an increased risk of calcium oxalate urolithiasis of more than threefold.[13,15] Water source and locality do not appear to be associated with calcium oxalate formation.

Nutritional Factors

Multiple epidemiological studies have identified nutritional risk factors associated with calcium oxalate urolithiasis.[13-15] Despite variation in study design, population studied, and study time period, results have been remarkably consistent.

Obesity

Obesity is associated consistently with an increased risk of lower urinary tract disease in cats. Overweight cats have nearly three times the risk for calcium oxalate urolithiasis as lean cats.[19] A clear pathophysiological mechanism linking obesity to urolith risk is lacking. Hypotheses include increased dietary mineral intake or prolonged urine retention in overweight, sedentary cats. Alternatively, the general risk factors for obesity may be similar to those for urolithiasis.

Feeding Method

Cats fed in the free-choice method often eat several small meals daily and avoid the large fluctuations in urine pH associated with a postprandial alkaline tide. Therefore the average urine pH of cats eating ad libitum is more acidic than those meal-fed the same food. Epidemiological studies in cats suggest an association between meal-feeding and reduced risk for calcium oxalate urolithiasis.[13,14] This risk reduction may be associated with an increased urine pH related to reduced meal frequency or a reduced risk of obesity associated with restricted food intake.

Urine Acidification

Although not all cats with acidic urine are at risk for calcium oxalate urolithiasis, aciduria contributes to several pathophys-

iological mechanisms that favor calcium oxalate urolith formation. Urine acidification has been identified as the strongest risk factor for the development of feline calcium oxalate uroliths. The odds of developing a calcium oxalate urolith increase linearly as the urine acidifying potential of the diet increases.[19] Certain drugs and dietary supplements also can lead to acidic urine. Urine acidification, by dietary consumption or drug administration, increases the calcium oxalate risk by 5 to 20 times.[13,19]

Food Moisture

Feeding high-moisture foods such as canned foods is associated with a threefold reduction in urolith risk.[19] Cats fed canned foods produce an increased volume of dilute urine compared with those fed dry food products.

Nutrient Concentration

In the 1980s the nutritional profile of many commercial cat foods was altered to reduce struvite urolith risk. To reduce magnesium, ammonium, phosphate excretion, many manufacturers reduced levels of magnesium and phosphorus in the foods and increased potassium, sodium, and urine-acidifying ingredients. These changes coincided temporally with the increased prevalence of feline calcium oxalate uroliths. A reciprocal relationship does not appear to exist between many dietary components that reduce struvite uroliths and those that increase calcium oxalate risk.[19] Although cats with calcium oxalate uroliths more commonly are fed foods with lower protein, calcium, phosphorus, magnesium, sodium, potassium, and moisture,[19] all of these components are not related reciprocally to increased risk of struvite urolithiasis. The exception is dietary urine acidifying potential, which is associated reciprocally to urolith composition.[19] An elevated urine pH is a risk factor for struvite urolithiasis, whereas more acidic urine increases the risk for calcium oxalate urolithiasis. Dietary levels of carbohydrate, fat, fiber, and chloride were not associated with the occurrence of calcium oxalate uroliths.

DIAGNOSIS

Clinical signs of calcium oxalate uroliths are similar to other urinary tract disorders. However, therapeutic and prevention protocols often have opposing strategies depending on urolith composition. Therefore, accurate diagnosis of urolith composition before initiation of specific nutritional therapy is paramount.

A detailed history, physical examination, imaging studies, complete blood count, serum biochemistry, urinalysis, and urine culture should be performed to screen for metabolic derangements occurring as a consequence of urinary tract obstruction or disorders that predispose toward calcium oxalate formation (e.g., renal failure or hypercalcemia) (see Chapters 17, 41, and 43). Special attention should be paid to the urinalysis for the presence of crystals, urinary pH, and specific gravity. Baseline assessments of these values also are valuable later during evaluation of the efficacy of preventive protocols. Quantitative analysis of voided or retrieved uroliths provides the most information about the mineral composition of uroliths.[20] An in-depth discussion of diagnostic evaluation of urolithiasis can be found elsewhere.[8]

TREATMENT

Medical protocols that promote dissolution of calcium oxalate uroliths are not available currently; therefore these uroliths must be removed physically. Voiding urohydropropulsion or catheterization may be used to retrieve small cystouroliths or urethroliths. For larger uroliths, a cystotomy must be performed. If urethral obstruction is present, urethroliths should be retropulsed into the urinary bladder. Occasionally, urethroliths cannot be retropulsed because of the irregular surface contour of calcium oxalate uroliths. If located in the distal penile urethra, a perineal urethrostomy may be necessary if gentle digital massage and retropulsion will not dislodge the urolith. When uroliths are not causing clinical signs and surgery is not an option, measures may be taken to prevent further increase in size and/or number (see section on prevention). Upper tract uroliths are increasingly common in cats[21] and should be removed if they are causing hematuria, pain, persistent bacterial infection, obstruction, or progressive renal damage. Often preventative measures are employed to minimize an increase in urolith size and number while monitoring for occurrence of these clinical signs by abdominal radiography every 3 to 6 months. Management considerations for upper urinary tract uroliths are discussed in Chapters 41, 43, and 44 in this volume and elsewhere.[22,23]

PREVENTION

Nutritional and/or medical protocols should be considered to minimize urolith recurrence or prevent further growth of uroliths remaining in the urinary tract (Figure 46-4). An estimated 30 per cent of cats develop recurrent uroliths within 2 years of their initial episode if preventive protocols are not initiated.[24] If possible, metabolic factors known to increase calcium oxalate risk should be corrected or minimized.

Dietary Considerations

The goals of dietary preventive strategies are to (1) reduce urine calcium and oxalate concentration, (2) promote high concentrations and activity of urolith inhibitors in urine, (3) reduce urine acidity, and (4) promote dilute urine.

Water

Increasing urine volume is a mainstay of preventative therapy for calcium oxalate urolithiasis in human beings. An increase in water intake reduces urine volume and concentrations of calculogenic minerals. In addition, larger urine volumes typically increase urine transit time and voiding frequency, which thereby reduces retention time for crystal formation and growth. Feeding cats a canned food is the most practical means of increasing water intake and lowering calcium oxalate urine saturation. The goal is to create urine with a specific gravity of 1.030 or less.[25] Flavoring water with diluted meat broths, enhancing water access, and adding water to dry foods may be used in cats that refuse to eat canned foods. Sodium chloride should not be added routinely to the diet in an effort to stimulate thirst. Although cats increase water intake and dilute urine in response to salt, the long-term consequences of high sodium intake in cats prone to calcium oxalate urolithiasis are unknown. Increased dietary sodium may increase urinary

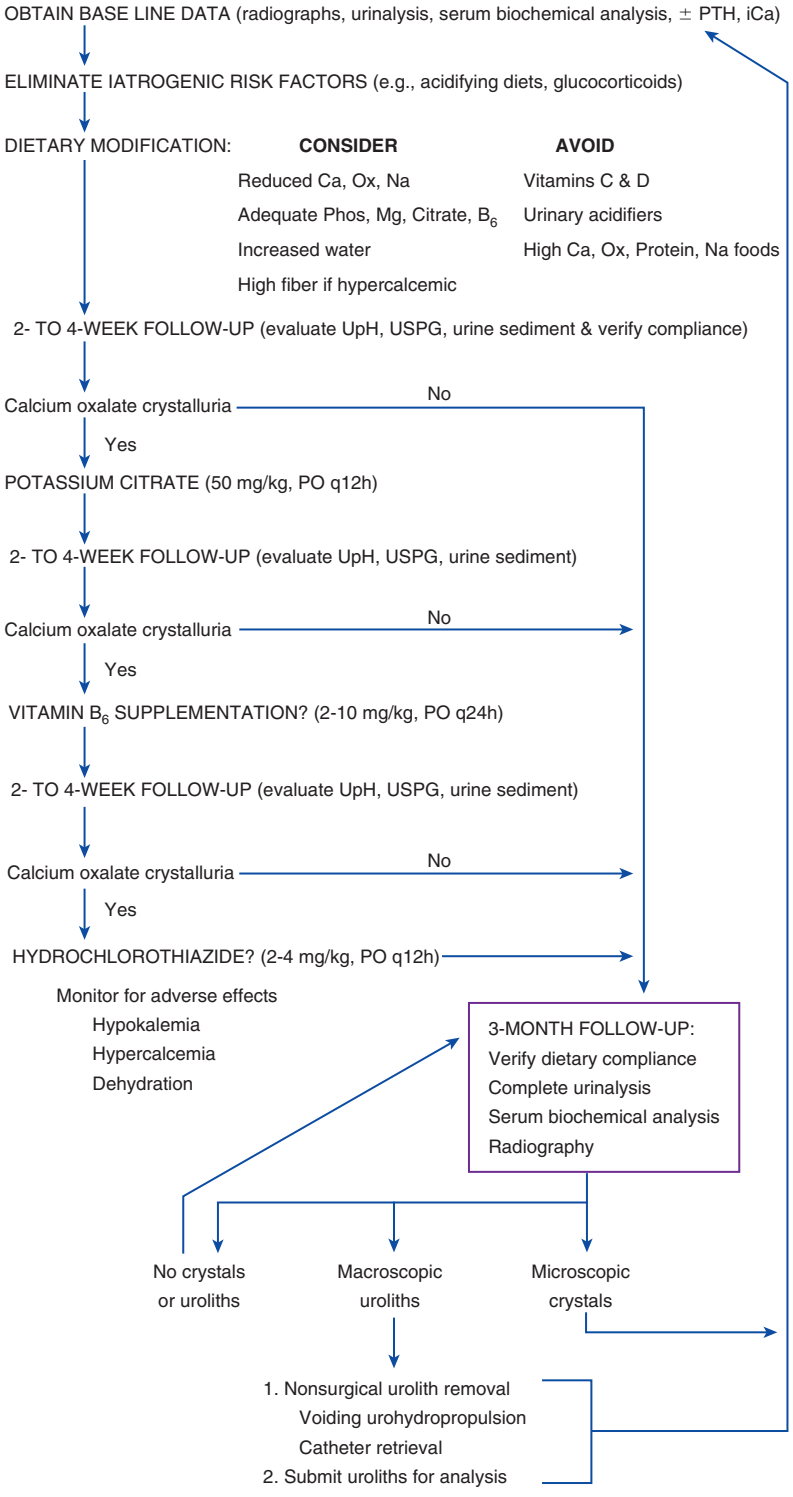

Figure 46-4. Algorithm for managing feline calcium oxalate uroliths. *Ox,* oxalate; *Phos,* phosphorus; *Na,* sodium; *Mg,* magnesium; *PTH,* parathyroid hormone concentration; *iCa,* ionized calcium; *UpH,* urine pH; *USPG,* urine specific gravity.

calcium excretion, and can contribute to ongoing renal damage in cats with marginal renal function.[25]

Acidifying Diets

Solubility of calcium oxalate in urine is influenced minimally by pH; however, epidemiological studies consistently identify acidifying diets as the most prominent risk factors for calcium oxalate urolithiasis.[13-15] Persistent aciduria may be associated with low-grade metabolic acidosis, which promotes bone mobilization and increases urinary calcium excretion. In a case series of five cats with hypercalcemia and calcium oxalate uroliths, discontinuation of acidifying diets or urinary acidifiers was associated with normalization of serum calcium concen-

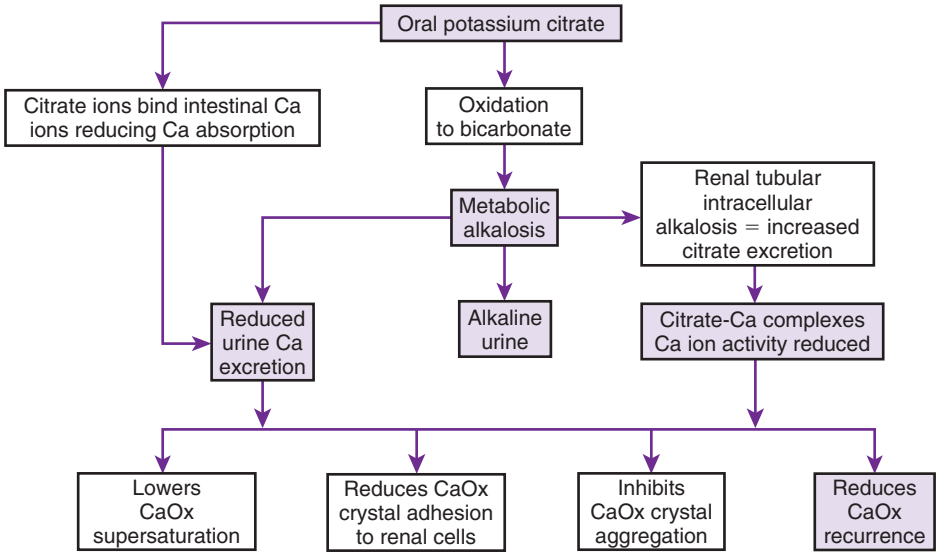

Figure 46-5. Influence of oral citrate supplementation on calcium oxalate (CaOx) urolith prevention.

tration.[26] Furthermore, aciduria promotes hypocitraturia and functional impairment of endogenous urolith inhibitors. Therefore feeding an acidifying diet or administering urinary acidifiers to cats at risk for calcium oxalate is contraindicated. A target urine pH of 6.6 to 7.5 is suggested in cats at risk for recurrent calcium oxalate uroliths.[25]

Calcium and Oxalic Acid

Although reduction of urine calcium and oxalic acid concentrations by restriction of dietary calcium and oxalic acid appears logical, it is not without concern. Reducing consumption of only one of these constituents may increase the availability and intestinal absorption of the other, which results in increased urinary excretion. Conversely, increasing dietary calcium levels in normal cats contributes directly to increased urine calcium concentration. Because epidemiological data in cats suggest marked dietary calcium restriction increases urolith risk, moderate levels of dietary calcium are advised in nonhypercalcemic cats.[25] In hypercalcemic cats, feeding foods with reduced levels of vitamin D and calcium and increased fiber levels has been useful to reduce hypercalcemia.[26]

Oxalic Acid

Urinary oxalate is derived from endogenous metabolism of oxalate precursors (i.e., glycine and ascorbic acid) and dietary oxalic acid. Most pet food ingredients are low in oxalic acid, with the exception of vegetables, legumes, and several vegetable-based fermentable fibers (i.e., beet pulp and soybean fiber). Dietary oxalic acid concentrations in foods for cats should be reduced to the lowest possible level. Suggested levels are less than 20 mg oxalic acid/100 g of food (dry matter basis).[25]

Excess intake of vitamin C, an oxalate precursor, similarly should be avoided.[25] Although normal dietary vitamin C levels are not considered a risk in human beings, even small increases in urinary oxalate that may result from additional vitamin C intake are a concern in urolith formers. Because cats do not have a dietary vitamin C requirement, supplementation should be avoided in foods fed to cats at risk for calcium oxalate uroliths. Cranberry concentrate tablets similarly are contraindicated. Cranberry extracts provide mild acidification and are high in oxalate, in addition to vitamin C.[27]

Citrate

Potassium citrate often is included in the diets designed for calcium oxalate prevention. In urine, citric acid combines with calcium to form soluble complexes and thereby reduces ionic calcium concentration. Citric acid also directly inhibits nucleation, aggregation, and growth of calcium and oxalate crystals in urine. Hypocitraturia is a risk for calcium oxalate urolithiasis in human beings. When citrate is oxidized within the Krebs cycle, bicarbonate is produced and results in metabolic and urine alkalinization. Metabolic alkalinization increases urine citrate concentrations by reducing renal tubular citrate reabsorption, and decreases hypercalciuria by reducing calcium excretion at the distal renal tubules[25] (Figure 46-5). Commercial pet foods that add citrate but continue to acidify the urine (pH less than 6.5) circumvent the benefit of citrate therapy.

Sodium

Consumption of high sodium levels may augment renal calcium excretion in human beings. In recent studies of healthy cats, high dietary salt intake (1.1 per cent dry matter) did not lead to increased urine calcium excretion.[25] In cats with marginal renal function and increased calciuria, however, high sodium intake exacerbated calcium excretion.

No studies have evaluated the effect of sodium intake specifically in cats naturally prone to calcium oxalate stone formation. Epidemiological evidence suggests that low dietary sodium levels in cat foods increase the risk for calcium oxalate urolithiasis.[19] Nonetheless, when fed a food lower in sodium (0.067 g/100 kcal vs. median 0.072 g/100 kcal), 10 cats with naturally occurring calcium oxalate uroliths excreted less urine calcium.[24] Until further data are available, orally administered sodium chloride or loop diuretics (which enhance renal sodium excretion) to promote diuresis should be used with caution and

careful monitoring, because the risk of calcium oxalate urolith formation may increase in some patients. The recommended level of sodium in foods for cats predisposed to calcium oxalate formation is between 0.3 and 0.5 per cent on a dry matter basis.

Phosphorus

Low dietary phosphorus is a risk factor for calcium oxalate urolith formation in cats.[19] Dietary phosphorus should not be restricted in cats with calcium oxalate urolithiasis. Reduction in dietary phosphorus may be associated with activation of vitamin D, which in turn promotes intestinal calcium absorption and hypercalciuria. Additionally, phosphate intake influences urinary concentrations of pyrophosphate, an inhibitor of calcium oxalate urolith formation. If calcium oxalate urolithiasis is associated with hypophosphatemia and normal calcium concentration, oral phosphorus supplementation may be considered. Caution should be used, however, because excessive dietary phosphorus may predispose to formation of calcium phosphate uroliths, although it is unknown if this consequence occurs in cats. Phosphorus levels in foods for cats predisposed to calcium oxalate formation should not be excessive; dietary levels of 0.5 to 0.8 per cent (dry matter) have been recommended.[25]

Magnesium

Urinary magnesium forms complexes with oxalic acid, which reduces the amount of oxalic acid available to form calcium oxalate precipitates. Studies in cats associate low dietary magnesium with calcium oxalate risk.[14,19] In human beings, supplemental magnesium has been used to minimize recurrence of calcium oxalate uroliths; however, supplemental magnesium may increase the risk of struvite precipitation in cats. At this time, the risks and benefits of magnesium supplementation to cats with calcium oxalate urolithiasis have not been evaluated, and this strategy is not advised. Magnesium likely should not be highly restricted in diets consumed by cats at risk for calcium oxalate urolithiasis. Many diets that claim to benefit feline "urinary tract health" are reduced in magnesium and promote urinary acidification. These foods are designed for struvite urolith prevention and are not appropriate for cats at risk for calcium oxalate urolithiasis. Prudent levels of dietary magnesium are 0.08 to 0.10 per cent dry matter or approximately 20 mg magnesium/100 kcal.[19,25]

Protein

Consumption of high amounts of animal protein by human beings is associated with an increased risk of calcium oxalate formation. Dietary protein of animal origin may increase urinary calcium and oxalic acid excretion, decrease urinary citrate excretion, and promote bone mobilization to buffer the acid intake from metabolism of animal proteins. However, an epidemiological study found that higher protein concentration in cat foods was protective against calcium oxalate uroliths.[19] Protein levels between 8 and 9 g/100 kcal appeared most protective. A possible explanation for this protective relationship is that high protein intake in cats can increase GFR and urine production. Increased urine volume may result in urine dilution or increased voiding frequency. Alternatively, increased protein intake simply may be a co-association of the high protein levels found in canned foods. Canned foods are known to cause more dilute urine and to decrease urine saturation with calcium and oxalate because of the high moisture content. Regardless of the mechanism, cats are obligatory carnivores, and dietary protein restriction in the management of calcium oxalate urolithiasis is not advised.

Vitamins D, C, and B_6

Excessive levels of vitamin D (which promotes intestinal absorption of calcium) and vitamin C (which is a precursor of oxalic acid) should be avoided. For vitamin D, foods providing between 500 and 2000 IU/kg dry matter should suffice. As discussed in previous sections of this chapter, vitamin C is an oxalate precursor and a weak urinary acidifier. Both features may increase the likelihood of urolith recurrence. The diet should be adequately fortified with vitamin B_6, because vitamin B_6 deficiency promotes endogenous production and subsequent urinary excretion of oxalic acid.[11] No evidence exists that providing increased vitamin B_6 beyond meeting the nutritional requirement provides a benefit in cats. Because most commercial diets designed for cats are well fortified with vitamin B_6, it is unlikely that additional supplementation is beneficial except for cats consuming homemade diets. Regardless, vitamin B_6 administration is reasonably safe and sometimes provided to cats with persistent calcium oxalate crystalluria or frequent recurrences in an attempt to minimize all potential risk factors.

Fiber

Increased dietary fiber intake is associated with decreasing risk of calcium oxalate recurrence in some human beings but not in cats. Certain types of fiber (soy or rice bran) decrease calcium absorption from the gastrointestinal tract, which may decrease urinary calcium excretion. In five cats with idiopathic hypercalcemia and calcium oxalate uroliths, feeding a high-fiber diet resulted in normalization of serum calcium concentrations.[26] However, the efficacy of increased fiber intake in prevention of urolith formation is unproven at this time.

Probiotics

Certain populations of enteric microbes are known to metabolize oxalic acid; of note is the bacterium *Oxalobacter formigenes,* which relies exclusively on oxalate for energy production. Low to absent enteric levels of *O. formigenes* have been reported in human beings with calcium oxalate uroliths.[28] Clinical trials feeding *Oxalobacter* probiotic resulted in increased enteric *Oxalobacter* levels but were ineffective in preventing urolith recurrence in human beings. At present, no evidence suggests that *Oxalobacter* spp. or any other oxalate-degrading microbe is a normal inhabitant of the feline enteric flora or that similar probiotic administration is beneficial in oxalate prevention in this species.

Obesity Prevention

Although the mechanisms relating obesity to calcium oxalate urolith formation in cats are not understood, obesity remains a consistent epidemiological risk factor. Overweight cats have

Table 46-1 | **Comparison of Diets Formulated for Prevention of Calcium Oxalate Urolithiasis in Cats**

COMPONENT	x/d DRY*	x/d CANNED*	PH/O DRY†	PH/O CANNED†	S/O DRY‡	S/O CANNED‡
MOISTURE						
As fed (per cent)	8	76	10	78	7	79
PROTEIN						
As fed (per cent)	31.3	10.5	32.4	10.6	32.2	8.5
Dry matter (per cent)	34.0	42.9	36.0	48.3	34.6	40.5
g/100 kcal ME	8.3	8.8	7.7	9.2	7.8	8.3
FAT						
As fed (per cent)	15.3	4.8	16.5	6.9	17.5	9.1
Dry matter (per cent)	16.6	19.6	18.3	31.2	18.0	43.1
g/100 kcal ME	4.1	4.0	3.9	5.9	4.2	8.8
FIBER						
As fed (per cent)	0.8	0.6	1.7	0.2	3.0	0.51
Dry matter (per cent)	0.9	2.4	1.9	1.0	3.2	2.4
g/100 kcal ME	0.2	0.5	0.4	0.2	0.7	0.5
SODIUM						
As fed (per cent)	0.33	0.09	0.44	0.11	1.3	0.2
Dry matter (per cent)	0.36	0.37	0.49	0.5	1.4	1.0
g/100 kcal ME	0.09	0.08	0.10	0.10	0.32	0.20
CALCIUM						
As fed (per cent)	0.70	0.17	1.01	0.27	1.0	0.21
Dry matter (per cent)	0.76	0.69	1.12	1.23	1.1	1.0
g/100 kcal ME	0.19	0.14	0.24	0.23	0.24	0.20
PHOSPHORUS						
As fed (per cent)	0.61	0.13	0.87	0.20	0.8	0.28
Dry matter (per cent)	0.66	0.53	0.97	0.91	0.86	1.33
g/100 kcal ME	0.16	0.11	0.21	0.17	0.19	0.27
MAGNESIUM						
As fed (per cent)	0.07	0.02	0.08	0.02	0.07	0.02
Dry matter (per cent)	0.08	0.08	0.09	0.14	0.08	0.09
g/100 kcal ME	0.02	0.02	0.02	0.02	0.02	0.02

Dry matter = percentage of nutrient in product after moisture is removed.
g/100 kcal ME = nutrient intake for every 100 kcal of metabolizable energy consumed.
*Prescription Diet Feline x/d = Nutrient information for diets as of Nov 2004; Hill's Pet Nutrition, Inc, Topeka, KS.
†Moderate pH/O/Feline = Nutrient information for diets as of July 2003; Iams Company, Dayton, OH.
‡Urinary S/O = Nutrient information for diets as of Nov 2004; Royal Canin, St. Charles, MO.

nearly three times the risk of developing uroliths (either struvite or calcium oxalate) compared with lean or underweight cats. Restricting food intake to obtain an ideal weight and body condition score (5/9 or 3/5) should be encouraged.

Feeding Method

Cats that are meal-fed have a more alkaline average urinary pH, eat a controlled amount of food (minimizing obesity), and are at a lower risk for calcium oxalate urolith formation than cats fed ad libitum. Meal-feeding also is the preferred method for feeding high-moisture canned foods, which also help prevent urolithiasis and other lower urinary tract disorders. Using a meal-feeding strategy is a relatively simple step that owners can take to improve prevention outcome.

Available Diets

At the time of this writing, three therapeutic foods are formulated and marketed for the prevention of calcium oxalate uroliths in cats (Table 46-1). These diets either contain potassium citrate and are designed to induce a higher urine pH when compared with standard foods or are designed to promote significant increases in water intake. Consumption of Prescription Diet Feline x/d (Hill's Pet Nutrition, Inc., Topeka, KS) or Urinary SO (Royal Canin, St. Charles, MO) by healthy cats results in low urine saturation with calcium oxalate. Clinical trials using Feline x/d in cats with naturally occurring calcium oxalate urolithiasis reduced calcium oxalate supersaturation by 59 per cent.[24] The reduction in calcium oxalate activity product ratio appeared to be a function of its ability to lower urine calcium. We also have had some success in reducing mild hypercalcemia in calcium oxalate urolith-forming cats by feeding a high-fiber diet (Prescription Diet Feline w/d; Hill's Pet Nutrition, Inc, Topeka, KS) and administering supplemental potassium citrate.

Pharmacological Treatment

Occasionally, dietary management is not sufficient to control calcium oxalate crystalluria or urolithiasis. Several pharmacological agents have been used in human beings and dogs and may be beneficial in cats with recurrent or progressive calcium oxalate uroliths.

Citrate

As indicated in earlier sections, urinary citrate inhibits calcium oxalate crystal formation and is an excellent urinary alkalinizer. If an appropriate urinary pH is not achieved by dietary management alone, additional oral potassium citrate may be beneficial. Potassium citrate is administered at a starting dose of approximately 50 mg/kg PO q12h. Dosage is titrated by monitoring urine pH, with the target urine pH between 7.0 and 7.5.

Vitamin B_6

Vitamin B_6 increases transamination of glyoxylate, a precursor of oxalic acid, to glycine. Although experimentally induced vitamin B_6 deficiency resulted in renal precipitation of calcium oxalate and hyperoxaluria in kittens,[11] a naturally occurring form of this syndrome has not been observed. Although the ability of supplemental vitamin B_6 to reduce urinary oxalic acid excretion in cats with calcium oxalate urolithiasis is unknown, supplementation is inexpensive and safe. It may be considered in cats with calcium oxalate uroliths that are difficult to manage. A dosage of 2 to 10 mg/kg PO q24h may be used.

Thiazide Diuretics

Thiazide diuretics are recommended to reduce recurrence of calcium-containing uroliths in human beings because of their ability to reduce urinary calcium excretion. The exact mechanism(s) by which thiazide diuretics achieve this effect is unknown. Studies in rats revealed that thiazide diuretics directly stimulated distal renal tubular reabsorption of calcium.[29] Although hydrochlorothiazide diuretics may be beneficial in minimizing urinary calcium excretion in human beings and dogs (2 to 4 mg/kg PO q12h),[17] these agents have not been evaluated in cats. Thiazide diuretic administration may be associated with adverse effects such as dehydration, hypokalemia, and hypercalcemia; therefore, their use cannot be recommended until further studies are performed.

Other Agents

Other agents have been used for management of calcium oxalate uroliths in human beings. *Allopurinol* has been used to minimize heterogeneous nucleation of calcium oxalate on uric acid crystals; however, this appears to occur rarely in cats. *Sodium cellulose phosphate* binds calcium in the intestinal tract, limiting its absorption; however, mechanism(s) of calcium oxalate formation including enteric hyperoxaluria in cats is unknown. *Orthophosphate* may minimize urinary calcium excretion. *Glycosaminoglycans* may act as urolith inhibitors and help prevent crystal adhesion to the urothelium. None of these agents have been evaluated in cats for the purpose of urolith prevention.

SUMMARY

To date, nutritional modification and increased hydration are the cornerstones of calcium oxalate prevention in cats. For cats with progressive or recurrent disease in the face of these strategies, additional pharmacological treatments, meal-feeding, and weight loss are recommended. Table 46-2 summarizes current

Table 46-2 | **Summary of Dietary Recommendations for Calcium Oxalate Prevention**

FACTOR	RATIONALE	RECOMMENDATION
Hydration therapy	Decreases urine concentration and saturation; increasing urine volume increases voiding frequency	Feed canned food or use other methods to increase water intake. Goal: urine specific gravity ≤1.030
Urine pH	Reduce hypercalciuria. Increase urine citrate. Potential impact on inhibitor function	Avoid acidifying foods or those with "urinary tract health" claims. Target urine pH between 6.6-7.5
Weight control	Reduces obesity	Maintain ideal body condition.
Protein	Target protein levels with low epidemiological risk Meet nutritional needs of cat. Control metabolic acids and hypercalciuria	Provide 8-9 g protein/100 kcal energy
Calcium	Reduce urine calcium saturation and block oxalate absorption in the intestines	0.5 to 0.8 per cent dry matter
Oxalic acid	Limit dietary oxalate intake to minimize urine oxalate saturation.	<20 mg oxalate/100 g dry matter
Sodium	Sodium may increase water intake and dilute urine; however, calciuric effect has been reported.	0.3 to 0.4 per cent dry matter
Phosphorus	Excessive reduction promotes intestinal calcium absorption. Pyrophosphate inhibits CaOx formation.	0.5 to 0.8 per cent dry matter
Citrate (potassium citrate)	Potent urine alkalinizer. Urine citrate is an inhibitor of crystal formation and binds to calcium.	Provide in food or as needed to achieve target urine pH levels. 50 mg/kg PO q12h
Magnesium	Magnesium forms complexes with oxalic acid, reducing urine oxalate saturation.	0.08 to 0.10 per cent dry matter or 20 mg/100 kcal
Vitamin B_6	Deficiency increases oxalate excretion. Required cofactor in oxalate metabolism.	Feed fortified food. Supplement as needed 2-10 mg/kg PO q24h
Vitamin D	Excess levels increase intestinal calcium and urine excretion	500-2000 IU/kg food dry matter
Ascorbic acid	Creates mild urine acidification and is metabolic precursor of oxalate	Do not supplement vitamin C Avoid vitamin C–fortified products
Fiber	May help bind intestinal calcium in cats with idiopathic hypercalciuria	Fiber fortified. Avoid high oxalate fibers (e.g., soy and beet fibers)
Feeding methods	Higher postprandial alkaline tide increases average urine pH to avoid aciduria. Prevent obesity	Meal-feed canned foods

recommended intakes of key nutrients for prevention of urolith recurrence or growth. Ongoing studies are sure to clarify the role of certain nutrients in the pathogenesis of calcium oxalate formation and to help define optimal intakes. Other nutrients identified by epidemiological studies as risk factors for calcium oxalate urolithiasis are sure to be acquitted. In the meantime, the best preventive approach addresses a broad scope of risk factors to achieve optimal outcome.

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Chapter 47

Etiopathogenesis of Feline Idiopathic Cystitis*

Jodi L. Westropp and C.A. Tony Buffington

Feline idiopathic cystitis (FIC) has been characterized as a chronic lower urinary tract syndrome of unknown cause and with no widely accepted treatment. The clinical signs of FIC include variable combinations of dysuria, pollakiuria, hematuria, and periuria (inappropriate urination). FIC may be the most common cause of lower urinary tract signs (LUTS). It affects two thirds of the 1.5 per cent of cats that present to primary care veterinarians with LUTS.[1]

This review suggests that FIC is not a single disease entity, presents the evidence for the comorbidity of a variety of unexplained clinical conditions in some patients with FIC, describes recent experimental results obtained in cats with severe FIC that reveal the presence of an underlying neuroendocrine abnormality in these patients, and shows how these results offer the possibility of additional therapeutic approaches for this subset of patients.

One of the most valuable resources for understanding such a cryptic disorder is the availability of a naturally occurring disease model in another species that permits investigations not possible in the target species. The most relevant naturally occurring model of FIC identified to date is interstitial cystitis (IC), a chronic pelvic pain syndrome of human beings characterized by pain referable to the urinary bladder and urinary frequency and urgency. Two presentations of IC are recognized based on cystoscopic evaluation of the bladder (although the necessity of cystoscopy for the diagnosis of IC is debated among urologists).[2] As in cats, only submucosal petechial hemorrhages are observed in most IC patients (type I), whereas ulcers occur within the dome and lateral walls of the bladder in a minority (<20 per cent) of human patients (type II), and only rarely in cats. Studies from human beings with IC and other chronic pain syndromes have helped us gain additional insight into abnormalities we have documented in cats with FIC.

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COMORBID CONDITIONS IN CATS WITH FELINE IDIOPATHIC CYSTITIS

Human patients with IC appear to suffer from a wide variety of comorbid conditions and the data suggest the same is true in cats. For example, LUTS have been reported to be a comorbid condition in cats with separation anxiety syndrome,[3] hypertrophic cardiomyopathy,[4] and obesity.[5] These findings suggest that FIC may not be a disease process localized to the bladder. Further research in cats with FIC supports this hypothesis. Clinicians must obtain a thorough history and physical examination of cats with LUTS to identify other abnormalities and to help prepare specific therapeutic protocols for individual cats with FIC.

One important challenge to any hypothesis for a non-bladder etiology for FIC is, "Why are clinical signs related to the urinary bladder?" A more illuminating question may be, "Why can so many organ systems be affected in patients with FIC and IC?" The answer to this question may be related to alterations in the two primary stress response systems in the body: the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis.

PATHOPHYSIOLOGY OF FELINE IDIOPATHIC CYSTITIS

Based on our research in cats with severe, recurrent FIC, we have documented an enhanced activation of the stress response system, primarily the SNS limb. A schematic diagram of the normal regulation of this complex neuroendocrine system[6] is presented in Figure 47-1. In summary, once stimulated by higher brain structures responding to the perception of a threat, corticotrophin-releasing factor (CRF) is released from the hypothalamus, which acts as a hormone to stimulate the anterior pituitary gland to release ACTH. CRF also acts as a neurotransmitter to stimulate neurons in the brainstem, including the locus coeruleus, to activate the sympathetic nervous system. Under mild stress conditions, cats with FIC had significantly higher plasma levels of dihydroxyphenylalanine (DOPA), norepinephrine (NE), and other catecholamine metabolites

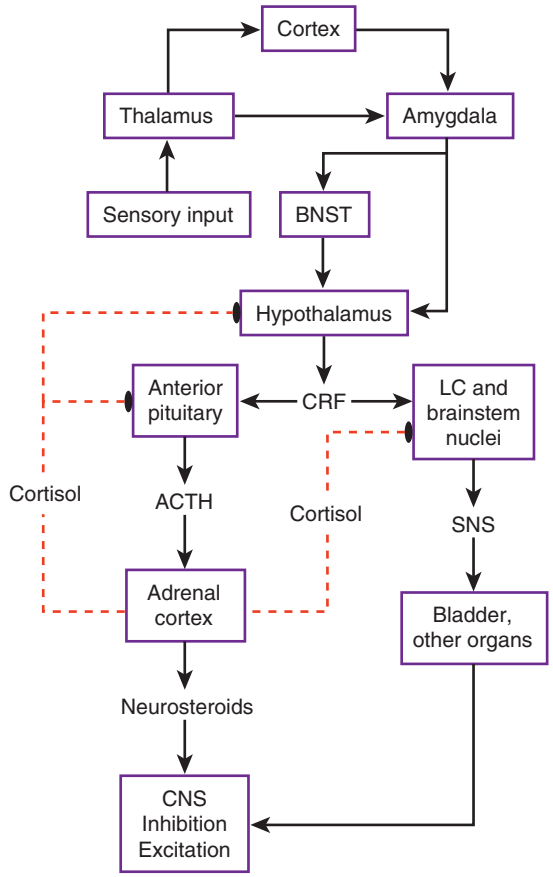

Figure 47-1. Normal balance of the CRF response system to stressors. In this case, excitatory SNS outflow from the locus coeruleus is restrained by cortisol. Cortisol also restrains the system by feedback inhibition at the level of the anterior pituitary gland and hypothalamus. The *solid lines* indicate stimulation, the *dotted lines* indicate inhibition.

compared with healthy cats.[7] These results support previous work documenting elevated tyrosine hydroxylase, the rate limiting step in catecholamine synthesis in the brainstem of cats with FIC.[8]

Activation of the SNS can increase epithelial permeability and permit environmental agents greater access to sensory afferent neurons, which could result in increased sensory afferent firing and local inflammation.[9] Altered bladder permeability has been reported in cats with FIC[10] and may be mediated via the SNS. Sympathoneural-epithelial interactions apparently play an important role in permeability. For example, Birder, Nealen, Kiss, et al[11] have shown that application of NE to urinary bladder (UB) strips induces release of nitric oxide from UB epithelium. Application of capsaicin results in release of NO from epithelium in addition to nervous tissue in the UB. In light of reports that NO may increase urothelial permeability,[12,13] these results suggest that some of the sympathetically mediated alterations in permeability may be mediated by NE via this mechanism. The increased permeability related to increased SNS activation does not require direct interaction with epithelial cells, nor is it restricted to the urinary bladder (Table 47-1).[14]

However, the presence of inflammation and altered permeability is not well correlated with pain, as anyone who has had a superficial bruise knows. In the bladder, we have reported the presence of submucosal petechial hemorrhages in cats with no signs referable to the lower urinary tract,[15] and other investigators have identified urothelial disruption and increased presence of inducible nitric oxide synthase (and presumably increased permeability) in painless bladder conditions.[16] Moreover, emotional and environmental factors such as stress or depression can modulate the experience of pain through descending pathways from the midbrain.[17] Therefore, even the increased activity of afferent nerves noted in FIC cats[18] could result in different perceived bladder sensations at any given time, depending on the emotional state of the animal.

If similar mechanisms are at work in patients with FIC, and the evidence to date suggests that they are, it could provide an explanation for the association of symptom flares with stressful circumstances. Conversely, drugs or environmental manipulations that promote improved emotional status, or are perceived to do so, are likely to reduce flare-ups. Such a mechanism also could explain the high placebo response (approximately 50 per cent) observed in IC and FIC drug trials.[19] Knowledge of this "placebo" response can be useful for the clinician, because maximizing it through environmental enrichment strategies described below could result in a more successful outcome for the patient.

Table 47-1 | **Neuroinflammatory Diseases in Human Beings**

DISEASE	PATHOPHYSIOLOGICAL EFFECTS
Asthma	Increased permeability, inflammation, bronchoconstriction
Atopic dermatitis	Increased permeability, inflammation, skin vasodilation, T cell recruitment, itching
Cardiovascular disease	Coronary inflammation
Chronic prostatitis	Prostate inflammation
Fibromyalgia	Muscle inflammation
Interstitial cystitis: type I	Increased permeability, atypical (no inflammatory infiltrate) inflammation, vasodilation and vascular leakage, urothelial damage
Interstitial cystitis: type II	Increased permeability, inflammation, urothelial damage
Irritable bowel syndrome	Increased permeability, inflammation, smooth muscle and myenteric plexus irritation
Migraines	Meningeal vasodilation and inflammation
Multiple sclerosis	Increased blood:brain barrier permeability, brain inflammation
Neurofibromatosis	Skin nerve growth, fibrosis
Osteoarthritis	Articular erosion and inflammation
Rheumatoid arthritis	Increased permeability, joint inflammation, cartilage erosion
Scleroderma	Skin inflammation and fibrosis

Many of these conditions coexist in the same patients.
Modified from Theoharides TC, Cochrane DE: Critical role of mast cells in inflammatory diseases and the effect of acute stress. J Neuroimmunol 146:1-12, 2004.

In contrast to the elevated SNS in some FIC cats,[20] we found that the cortisol response to ACTH stimulation was reduced during stressful periods in cats with FIC.[21] We also found that adrenal gland size was significantly smaller in cats with FIC than in healthy cats.[21] Microscopic examination of the adrenal glands did not reveal any obvious fibrosis, hemorrhage, inflammation, infection, or necrosis as causes of the reduced size; the primary abnormality identified was a reduced size of the zona fasciculata and zona reticularis (the zones responsible for cortisol and other steroid hormone secretions). These results, when combined with our observations of increased concentrations of CRF[22,23] and ACTH[24] in response to stress, in the absence of a comparable increase in plasma cortisol concentration, strongly support the presence of decreased adrenocortical reserve in cats with FIC. Cortisol normally restrains SNS outflow from the locus coeruleus and inhibits its own release by feedback inhibition at the level of the anterior pituitary gland and hypothalamus to terminate the stress response. The lack of cortisol (and possible other neurosteroids) might contribute to the elevated SNS. Adrenocortical steroids tend to antagonize the effects of the SNS. For example, glucocorticoids play a role in epithelial permeability, with cortisol primarily enhancing tight junction integrity to reduce permeability. This and other adrenocortical steroid-related protective mechanisms[25-27] may be less efficient in hypocortisolemic states.[28]

To explain this paradoxical combination of increased CRF, ACTH, and SNS activity is difficult in the presence of reduced adrenocortical response and small adrenal fasciculata and reticularis zones. One current hypothesis involves a genetic disorder or developmental anomaly affecting the fetus (or some combination of the two). A number of recent reviews have explored the consequences of subjecting pregnant females to threatening stressors for the developing fetus.[29-31] If the stressor is sufficiently harsh, the hormonal products of the ensuing stress response may cross the placenta and affect the course of fetal development. These relationships are depicted in Figure 47-2. A reduction in adrenal size may result from glucocorticoid-mediated suppression of release of ACTH by the fetal anterior pituitary gland. Recently, Leavitt, Aberdeen, Burch, et al reported that glucocorticoid injection during late gestation in baboons inhibited fetal pituitary ACTH release and adrenal cortical ACTH receptor expression.[32] They determined subsequently that this effect blocked development of the fetal transitional (cortisol-producing) zone.[33] Prenatal and postnatal stressors also can result in persistently increased central CRF activity.[34] Regardless of the cause, decreased biological activity of glucocorticoids may have a variety of adverse effects on bodily function, possibly related to their role in restraining activation of the immune system and other components of the stress response, including the SNS and CRF.

Although cortisol responses are subnormal in these severe FIC cats, cortisol replacement with prednisone has not been demonstrably useful in this clinical syndrome. The apparent lack of long-term benefit of glucocorticoid therapy in patients with FIC suggests that inadequate production of other steroids also may play a role in the pathophysiology of this disease. The adrenal cortex is responsible for many different hormones, and we have investigated only the most common one, cortisol. A review of hormone pathways from the adrenal gland is presented in Figure 47-3. Preliminary studies in human patients with IC have suggested alterations in the relationships between adrenal hormones, particularly the cortisol/dehydroepiandrosterone sulfate (DHEAS) ratio.[35] Adrenocortical function also has been evaluated in human patients with other chronic, waxing and waning pain conditions (e.g., chronic fatigue syndrome [CFS]) by measuring the cortisol/DHEAS ratio.[36] This ratio was twofold to threefold higher in CFS patients than in

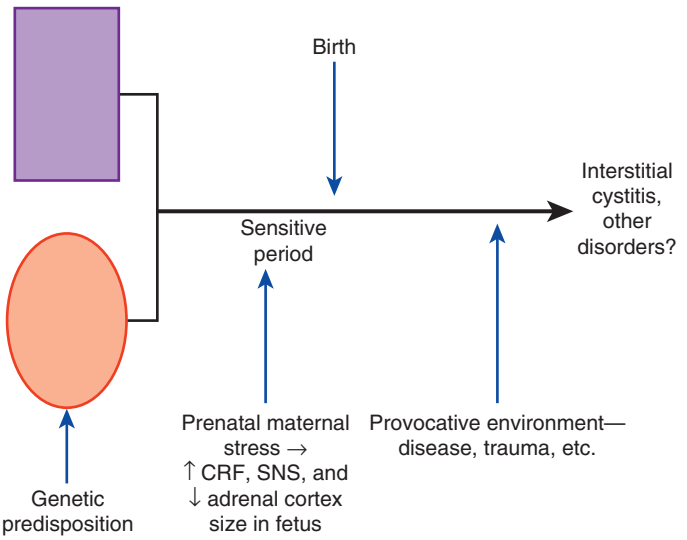

Figure 47-2. Hypothesized trajectories to IC. Variable combinations of these factors could result in differences in disease severity among patients.

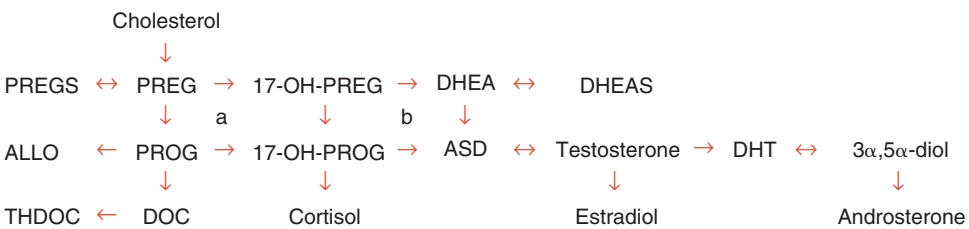

Figure 47-3. Some major recognized pathways of adrenocortical steroid synthesis. Other intermediate end products (not shown) also occur. The P450c17 enzyme *(a)* performs the 17α-hydroxylase reaction equally well using pregnenolone and progesterone as substrates, but the 17,20 lyase reaction occurs 50 to 100 times more efficiently using 17OH-Preg as substrate rather than 17OH-Prog. Therefore conversion of 17OH-Prog to androstenedione is minimal, and DHEA is the principal precursor of sex steroid synthesis.[55] *PREG,* pregnenolone; *PREGS,* pregnenolone sulfate; *17-OH-PREG,* 17-hydroxy-pregnenolone; *DHEA,* dehydroepiandrosterone; *DHEAS,* dehydroepiandrosterone sulfate; *ALLO,* 3α,5α-tetrahydroprogesterone; *PROG,* progesterone, *17-OH-PROG,* 17-hydroxy-progesterone; *ASD,* androstenedione; *DHT,* dihydrotestosterone; *3α,5α-diol,* 3α-androstanediol; *THDOC,* 3α,5α-tetrahydrodeoxycorticosterone; *DOC 11,* deoxycorticosterone.

controls. Kizildere, Gluck, Zietz, et al[37] have suggested that serum levels of DHEAS may be low in patients with inflammatory and noninflammatory diseases because of an activated SNS. They concluded that sympathetic hyperactivity may be a common denominator for low levels of DHEAS in both inflammatory and noninflammatory diseases. Currently, we have not investigated this in cats with FIC. In the meantime, we cannot advocate the use of steroids as a sole treatment for FIC, and based on clinical experience, cats do not seem to improve with the current antiinflammatory doses of prednisone commonly administered.

TREATMENT STRATEGIES

The sensitivity of cats to their surroundings has long been recognized.[38,39] Recent ethological studies in zoos,[40] research laboratories,[41] and boarding facilities[42] have documented that cats subjected to impoverished or unpredictable environments have decreased activity levels and increased hiding behaviors (see Chapter 76).

The indoor environment of some house cats also may be monotonous and predictable, which could be stressful.[43] The effects of indoor housing on disease risk in domestic cats recently have been reviewed.[44] Although it reduces the risk of infectious disease and accidental injury, indoor housing has been associated with increased risk (odds ratio) for development of LUTS, calcium oxalate urolithiasis, odontoclastic resorptive lesions (see Chapter 9), obesity (see Chapter 19), and hyperthyroidism.[44]

Currently, the HPA axis abnormalities found in cats with FIC are not fully understood, and our current therapy is aimed at alteration of the SNS in hopes of decreasing sympathetic tone and neurogenic inflammation and altered permeability. Any treatment strategy to decrease SNS outflow may be important in reducing these abnormalities. Our clinical experience with cats with severe FIC suggests that environmental enrichment to attempt to reduce the cat's perception of threat often is sufficient to eliminate recurrence of signs. We have reported recently that environmental enrichment strategies that consisted of owner education about their cat's disease, proper litterbox management strategies, dietary alterations, modification of the indoor environment to reduce anxiety, and cooperation with owners in multicat households to reduce conflict[45] resulted in highly statistically and clinically significant remission of LUTS *and* abnormal behavioral signs.[46] Changes to the cat's environment were implemented slowly, and alterations were tailored for each individual cat according to limitations of each owner and household. Owners were instructed or mailed information from a website developed to provide information on enhanced indoor environments for cats (www.indoorcat.org). A thorough strategy for helping owners understand FIC is crucial to maintaining client satisfaction when initiating a treatment regimen.

Another strategy for treating cats with FIC includes the application of feline pheromones. Pheromones are fatty acids that seem to transmit highly specific information between animals of the same species. Although the exact mechanisms of action are unknown, pheromones reportedly induce changes in the limbic system and the hypothalamus, which alter the emotional state of the animal.[47] Feliway (Ceva Sante Animale, Libourne, France), a synthetic analogue of this naturally occurring feline facial pheromone, was developed in an effort to decrease anxiety-related behaviors of cats. Although not specifically tested in cats with FIC, treatment with this pheromone has been reported to reduce the amount of anxiety experienced by cats in unfamiliar circumstances, a response that may be helpful for FIC patients and their owners.[48] Others have reported decreased spraying in multicat households[49,50] and a significant decrease in scratching behavior.[47] Although Feliway is not a panacea for unwanted cat behaviors or FIC, we have used it successfully in combination with environmental enrichment in some cats with FIC. Feliway is sold as a spray and room diffuser. The spray can be used to treat areas of the house where the cat is urinating by use of a single spray to the affected spot daily for 30 days. We have had encouraging anecdotal successes in the management of some FIC cats using Feliway.

CONCLUSION

FIC apparently is no longer a syndrome isolated solely to the bladder. Identification of involvement of other organ systems[51-54] suggests a role for central neuroendocrine involvement in at least some patients. FIC and the other unexplained clinical conditions with which it can be comorbid are so complex that is seems unlikely that all, or even most, cases can be explained by a single underlying etiology. Even if a neuroendocrine imbalance explains only a subset of cases, however, it could improve care for these patients and hopefully lead to alternative hypotheses for those cats that suffer from FIC resulting from other etiologies.

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Chapter 48

Revisiting Bacterial Urinary Tract Infection

Joseph W. Bartges

ETIOLOGY

A urinary tract infection (UTI) occurs when a breach (either temporary or permanent) in host defense mechanisms develops, and a virulent microbe in sufficient numbers is allowed to adhere, multiply, and persist in a portion of the urinary tract. Bacteria typically cause UTIs; however, fungi and viruses also may infect the urinary tract. Because a bacterial UTI may involve more than one anatomical location, it may be more relevant to identify the infection as upper urinary tract (kidneys and ureters) versus lower urinary tract (bladder, urethra, and vagina). The infection may or may not produce clinical signs.

EPIDEMIOLOGY

The reported incidence of bacterial UTI in cats is variable. In prospective studies that have evaluated lower urinary tract disease in young cats, bacterial UTIs were diagnosed in less than 2 per cent of cases.[1-3] In other studies, however, bacterial UTIs were found in 15 to 43 per cent of cats that were evaluated.[2] In one study, UTIs were present in 25 per cent of 1380 urine cultures performed at a university hospital over a 12-year period.[4] The average age of cats with bacterial UTI was 8.2 years; the average age of infected males was 6.3 years, whereas the average age of infected females was 10.6 years.[4] In a retrospective study performed at the University of Georgia and the University of Tennessee, bacterial UTI was identified in 45 per cent of cats older than 10 years with signs of lower urinary tract disease.[5] Two thirds of these cats also were diagnosed with renal failure, whereas the remaining cats had concurrent hyperthyroidism, corticosteroid or diuretic treatment, feline immunodeficiency virus and/or feline leukemia virus infection, urinary incontinence, or neoplasia.[5] When examined independently in another group of cats, chronic renal failure was accompanied by a bacterial UTI in approximately 20 per cent of cats.[6]

Findings from these studies indicate that bacterial UTI is uncommon in young cats with lower urinary tract disease, but bacterial UTI is an important problem in older cats.[7,8] Older cats may be at increased risk for development of bacterial UTI because of diminished urinary tract defenses. Whether impaired defenses are intrinsic to the aging process or secondary to disorders that are common in older cats is unknown. A reasonable hypothesis is that these conditions of older cats, such as renal failure, diabetes mellitus, and hyperthyroidism, impair normal defense mechanisms.

PATHOGENESIS

The pathogenesis of bacterial UTI represents a tipping of the balance between uropathogenic infectious agents and host resistance. UTIs, of course, can be treated with antimicrobial agents as they occur; however, the status of host defense mechanisms is important in development of a UTI and must be considered to plan successful treatment and prevention.

Normal Host Defenses

The urogenital tract communicates with the external environment. Most bacterial UTIs are due to ascending migration of pathogens from the distal urogenital tract into otherwise normally sterile locations. A resident population of bacteria normally is present in the lower urogenital tract, which may decrease establishment of a uropathogen or may emerge as a uropathogen if normal host defenses are altered.[9]

Although the urinary tract communicates with the microbe-laden external environment, under normal conditions most of the urinary tract is sterile, and all of it is resistant to infection. Mechanisms of host resistance to UTI include normal micturition, normal urinary tract anatomy, uroepithelial mucosal barriers, antimicrobial properties of urine, and systemic immunocompetency (Table 48-1).

Table 48-1 | **Natural and Acquired Host Defenses of the Urinary Tract**

NORMAL MICTURITION
Adequate urine volume
Frequent voiding
Complete voiding
ANATOMICAL STRUCTURES
Urethral high-pressure zones
Surface characteristics of urothelium
Urethral peristalsis
Prostatic secretions (antibacterial fraction and immunoglobulins)
Length of urethra
Ureterovesical flap valves
Ureteral peristalsis
Glomerular mesangial cells (?)
Extensive renal blood supply and flow
MUCOSAL DEFENSE BARRIERS
Antibody production
Surface layer of glycosaminoglycans
Intrinsic mucosal antimicrobial properties
Exfoliation of urothelial cells
Bacterial interference by commensal microbes of distal urogenital tract
ANTIMICROBIAL PROPERTIES OF URINE
Extreme high and low of urine pH
Hyperosmolality
High concentration of urea
Organic acids
Low-molecular-weight carbohydrates
Tamm-Horsfall mucoproteins
SYSTEMIC IMMUNOCOMPETENCE OTHERS?

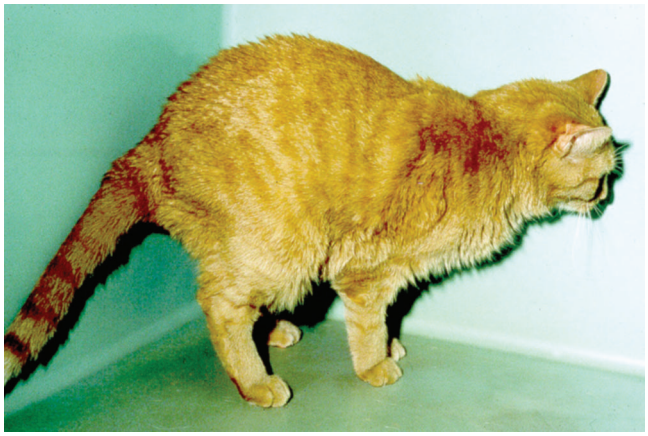

Figure 48-1. A 3-year-old castrated male cat demonstrating signs of lower urinary tract disease.

Microbial Factors

Not all bacteria are pathogenic. For example, of the more than several hundred serotypes of *Escherichia coli*, less than 20 account for the majority of bacterial UTIs.[10] Infections caused by pathogenic *E. coli* are most common and account for one third to two thirds of all organisms isolated from urine.[11-14] Gram-positive cocci are the second major group of uropathogens. *Staphylococcus* spp., *Streptococcus* spp., and *Enterococcus* spp. account for one fourth to one third of isolates recovered. Bacteria causing the remaining one fourth to one third of bacterial UTIs include *Proteus* spp., *Klebsiella* spp., *Pasteurella* spp., *Pseudomonas* spp., *Corynebacterium* spp., and *Mycoplasma* spp.; however, each of these types of bacteria has been reported in only a few instances of UTI in cats.[4,15-17] Approximately 75 per cent of bacterial UTIs in dogs are caused by a single pathogen, approximately 20 per cent are caused by two organisms, and approximately 5 per cent are caused by three species.[18] A similar pattern of infection is found in cats.[16,19]

Transmission

The majority of bacterial UTIs occur as a consequence of ascending migration of pathogens through the genital tract and urethra to the bladder, ureters, and one or both kidneys. Rectal, perineal, and genital bacteria are the principal reservoirs for infection.[20,21] In addition to gaining access to the urinary tract, microbes must adhere to and colonize the urothelial surface. Therefore, the establishment of a UTI depends on the virulence and number of microbes and their interaction with host defenses.

The upper urinary tract is infected most commonly by ascending microbes rather than through hematogenous routes. Renal cortical tissue appears to be more resistant to infection than medullary tissue. Because circulating blood must pass through glomerular capillaries located in the cortex before it reaches the medulla, most hematogenous bacteria do not reach the renal medulla. However, urinary tract obstruction or trauma can increase risk of hematogenous seeding of the urinary tract by interfering with renal microcirculation.[22]

CLINICAL SIGNS

Clinically, bacterial UTIs may be symptomatic or asymptomatic. Bacterial infection of the lower urinary tract usually is associated with clinical signs similar to other diseases of the lower urinary tract. These signs include, but are not limited to, pollakiuria, dysuria, stranguria, hematuria, and inappropriate urination (Figure 48-1). Bacterial UTI of the kidneys may be associated with hematuria; if septicemia develops, the cat may be systemically ill. In addition, upper UTIs may cause recurrent lower UTIs.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses for bacterial infection of the lower urinary tract disease in cats include urolithiasis, idiopathic cystitis, neoplasia, and behavioral disorders. Upper urinary tract signs, including renomegaly, renal pain, hematuria, or renal failure, may be caused by UTI or by many other primary renal disorders. Causes of renal failure are many and often determination of the role, if any, that a bacterial UTI plays in the development or progression of chronic renal failure in cats is impossible. If renomegaly is present, differential diagnoses should include feline infectious peritonitis, neoplasia (most notably lymphosarcoma), hydronephrosis resulting from ureteral obstruction (see Chapter 41), and polycystic kidney disease.

DIAGNOSIS

Urinalysis

A urinalysis should be performed as a routine part of a minimum database in older or ill cats. A complete urinalysis involves determining urine specific gravity (USPG) using a refractometer, biochemical analysis using colorimetric test pads on urine dipsticks, and microscopic sediment examination. Cystocentesis is the preferred method of urine collection in evaluation of a patient for a UTI. With UTI, the USPG is variable depending on whether the infection involves the upper urinary tract or an associated disease. Dipstick analysis often, but not always, reveals hematuria and proteinuria. Leukocyte esterase (white blood cells) and nitrite (bacteria) test pads are not reliable and should not be used as indicators of bacterial UTI in cats.[23]

Examination of urine sediment should be a routine part of a complete urinalysis. Significant numbers of white blood cells (≥5 per high-power field), along with hematuria and proteinuria, in a properly collected urine sample suggest inflammation. Detection of significant bacteriuria in samples with pyuria indicates active inflammation associated with an infection. Rod-shaped bacteria may be identified in unstained preparations of urine sediment if more than 10,000 bacteria/ml are present but may not be detected consistently if present in fewer numbers. Cocci are difficult to detect in urine sediment if their numbers are less than 100,000 bacteria/ml. Bacteria are more difficult to identify in dilute urine, which makes a diagnosis of UTI problematic in the face of polyuria. Urine sediment may be stained with Wright's stain (Figure 48-2),[24] Gram's stain, or new methylene blue to aid in detection of bacteria. Failure to detect bacteria on examination of urine sediment does not exclude their presence or rule out UTI. On the other hand, bacterial UTI may exist without concurrent inflammation if host defenses are compromised (e.g., feline leukemia virus infection).[16,25] Although detection of bacteria in urine sediment suggests bacterial UTI, bacterial infection should be verified by urine culture.

Urine Culture

A positive culture is the "gold standard" for diagnosing a bacterial UTI. A diagnosis based only on clinical signs, hematuria, or microscopic evidence of urinary tract inflammation is a misdiagnosis that may result in inadequate or inappropriate treatment. Samples for urine culture should be collected before initiation of therapy whenever possible. If antimicrobial therapy has been started, administration should be discontinued for 3 to 5 days before performing a urine culture to minimize the inhibition of microbial growth.

Care must be taken to collect, preserve, and transport the urine sample to avoid contamination or proliferation or death of bacteria.[26] Urine specimens for aerobic bacterial culture should be transported and stored in sealed, sterilized containers, and processing should begin as soon as possible. If laboratory processing is delayed by more than 30 minutes, the sample should be refrigerated (4° C).[27] When refrigerated, commercially available urine collection tubes containing preservative may be used to preserve specimens for up to 72 hours.[29] At room temperature, bacterial counts in urine may double every 20 to 45 minutes. Multiplication or destruction of bacteria may occur within an hour of collection.

If urine samples cannot be processed immediately for urine culture, alternative methods for sample handling are available. Blood agar and MacConkey's agar plates may be inoculated and incubated for 24 hours. A calibrated bacteriological loop or microliter mechanical pipette that delivers exactly 0.01 or 0.001 ml of urine can be used to inoculate the culture plates. The plates are streaked by conventional methods. Blood agar supports growth of most aerobic uropathogens (Figure 48-3); MacConkey's agar provides a medium that aids in identification of bacteria and prevents "swarming" of *Proteus* spp. The plates are placed in an incubator or under an incandescent light for 24 hours (Figure 48-4).[28,30] If bacterial growth is observed

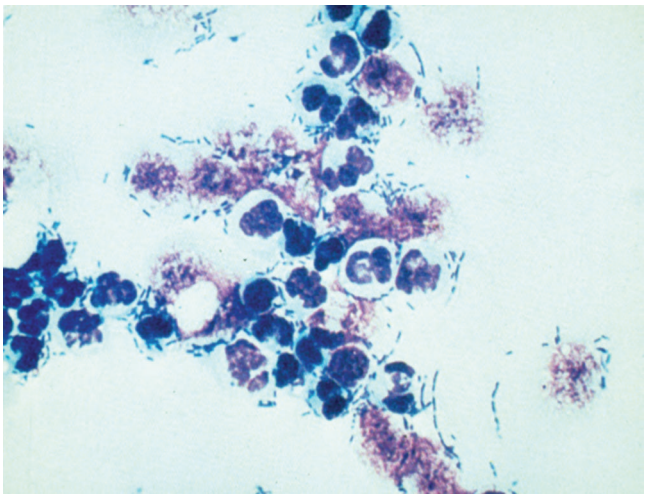

Figure 48-2. Photomicrograph of urine sediment stained with Wright's stain containing red blood cells, neutrophils, and bacterial rods. Aerobic bacterial urine culture revealed *Escherichia coli* (40× magnification).

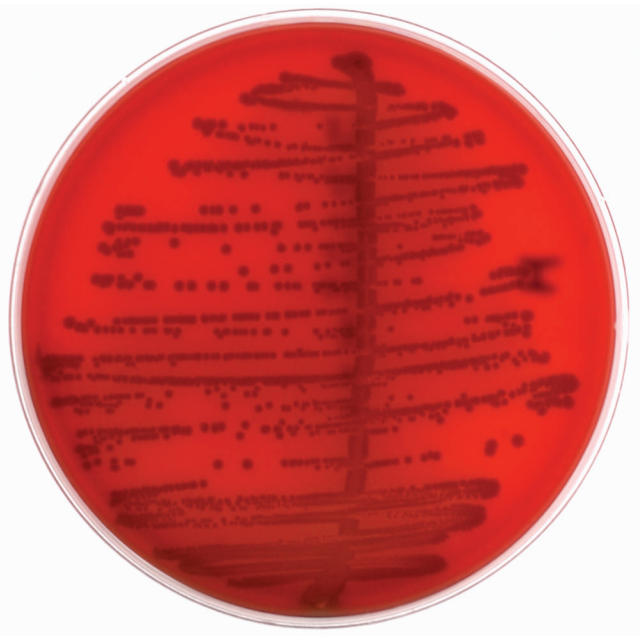

Figure 48-3. Bacterial growth on a blood agar plate inoculated with urine using a calibrated bacteriological loop after incubation at 37° C for 24 hours. Identification was *Escherichia coli*.

Figure 48-4. Incubation of an inoculated blood agar plate with urine under a 60-watt incandescent light bulb. Surface temperature of the blood agar plate is 37° C.

on the plate after this time period, the plate may be submitted for identification and determination of antimicrobial sensitivity results. Alternatively, antimicrobial susceptibility may be determined "in-house" using the agar disk diffusion method. The plates may be discarded if no growth occurs after 24 hours.

Qualitative Urine Culture

A qualitative urine culture involves isolation and identification of bacteria in urine; it does not include quantification of bacterial numbers. Although urine in the bladder normally is sterile, urine that passes through the distal urogenital tract often becomes contaminated with resident flora. Therefore, interpretation of bacteria in urine collected by catheterization or voiding often is difficult to interpret even with quantification of bacteria. For this reason, a diagnostic urine culture should include quantitation of bacterial numbers in addition to identification of the organism and antimicrobial susceptibility.

Quantitative Urine Culture

A quantitative urine culture includes isolation and identification of the organism and determination of the number of bacteria expressed as colony-forming units (CFU) per unit volume. Quantitation of bacteria enables interpretation as to the significance of bacteria present in a urine sample. Caution should be exercised in interpretation of quantitative urine cultures obtained by midstream voiding or manual expression of urine. Although urine obtained from most dogs without UTI was either sterile or contained less than 10,000 CFU per milliliter of urine, counts of 100,000 CFU or more per milliliter of urine occurred with sufficient frequency to make collection of urine by these methods unsatisfactory.[26] Lower numbers of organisms are considered significant in cats, because cats appear to be more resistant to UTI than dogs and human beings.

Antimicrobial Susceptibility Testing

Administration of antimicrobial agents is the cornerstone of treating UTI. The antimicrobial agent selected should be (1) easy to administer, (2) associated with few, if any, side effects, (3) inexpensive, (4) able to attain tissue or urine concentrations that exceed the minimum inhibitory concentration (MIC) for the uropathogen by at least fourfold, and (5) unlikely to affect the patient's intestinal flora adversely. The choice of antimicrobial agent is based on antimicrobial susceptibility testing. The agar disk diffusion technique is used most often to determine antimicrobial susceptibility. Antimicrobial dilution susceptibility tests are designed to determine the minimum concentration of an antimicrobial drug that will inhibit the growth of the uropathogen (MIC). Agar disk diffusion technique is adequate for most cases of bacterial UTI; however, antimicrobial dilution technique may be required when a highly resistant organism is present.

Additional Diagnostic Evaluation

Because most cats with bacterial UTIs have complicated infections, other laboratory testing and imaging studies often are required. Logical choices include thyroid hormone and viral testing, in addition to abdominal radiographs and sonography. Depending on the predisposing or associated condition with the bacterial UTI, results of these tests may be abnormal.

TREATMENT

Uncomplicated Bacterial Urinary Tract Infections

Uncomplicated bacterial UTIs are lower tract infections in which no underlying structural, neurological, or functional abnormality is identified. Uncomplicated UTIs usually are treated successfully with a 10-day to 14-day course of an appropriate antimicrobial agent. If the proper antimicrobial is chosen and administered at the appropriate dosage and frequency, clinical signs should resolve within 48 hours. Additionally, results of a complete urinalysis should improve within this same time frame. If possible, a urine culture should be performed 5 to 7 days after cessation of antimicrobial therapy. Uncomplicated infections are rare in cats because of their inherent resistance to bacterial UTIs, and because infections typically occur with a predisposing cause.

Complicated Bacterial Urinary Tract Infections

Many cats have identifiable predisposing causes for bacterial UTIs (e.g., renal failure, diabetes mellitus) and should be considered to have a *complicated* bacterial UTI. Antimicrobial treatment continuing longer than the routine 10 to 14 days is indicated, usually 4 to 6 weeks. Urine should be evaluated in the first week of treatment for response to therapy and before therapy discontinuation. After antimicrobial therapy, prophylactic antibiotic treatment may be necessary to control bacterial UTIs that are difficult to eradicate or are frequently recurrent.

Recurrent Bacterial Urinary Tract Infections

Relapse

A relapse is defined as recurrence of a bacterial UTI resulting from the same organism. Relapses usually occur within days to

weeks of discontinuation of antimicrobial therapy, and are due to failure to eradicate the organism. Possible causes include use of an inappropriate antimicrobial agent; administration of an appropriate antimicrobial agent at the inappropriate dosage, frequency, or duration; or complicating factors. A urine culture should be evaluated before antimicrobial therapy is reinstituted. Additionally, further diagnostic evaluation for predisposing causes or a nidus of infection is indicated.

Reinfection

A reinfection is defined as a recurrence caused by a different organism than was initially present. Reinfections usually occur at a later time (weeks to months) after cessation of antimicrobial therapy. Although predisposing risk factors may be present, some animals that become reinfected often do not have identifiable risk factors. If reinfections are infrequent, each episode may be treated as an uncomplicated bacterial UTI. However, if reinfections occur at a frequency of more than three per year, then affected cats should be treated as having a complicated bacterial UTI. Additionally, prophylactic antimicrobial therapy may be indicated.

Superinfection

A superinfection occurs when a second bacterial organism is isolated while an animal is receiving antimicrobial therapy. Often this organism displays a high degree of antibiotic resistance. A bacterial UTI that occurs in animals receiving antimicrobial therapy that also have an indwelling urethral catheter is another example of a superinfection.

Prophylactic Antimicrobial Treatment

No studies have thoroughly evaluated prophylactic antimicrobial therapy in animals with frequent reinfections. Before prophylactic treatment is undertaken, results of urine culture and susceptibility testing should be examined to ensure that the bacterial UTI has been eradicated. For long-term prophylaxis, a drug is selected that is excreted in high concentration in urine and that is unlikely to cause adverse effects. Often a fluoroquinolone, a cephalosporin, or a β-lactam antimicrobial is chosen. The antimicrobial agent is administered at approximately one third of the therapeutic daily dose immediately after the patient has voided, at a time when the drug and its metabolites will be retained in the urinary tract for 6 to 8 hours (typically at night). The drug is given for a minimum of 6 months. Urine samples, collected preferably by cystocentesis (not by catheterization as this may induce a bacterial UTI), are collected every 4 to 8 weeks for urinalysis and quantitative urine culture. If the sample is free of bacterial UTI, prophylactic treatment is continued. If a bacterial UTI is identified, active (breakthrough) infection is treated as a complicated bacterial UTI before return to a prophylactic strategy. If a breakthrough bacterial UTI does not occur after 6 months of prophylactic antimicrobial therapy, treatment may be discontinued and the patient monitored for reinfection.

Prevention of Iatrogenic Infection

Normal host defense mechanisms are effective in preventing bacterial UTIs; however, they are not impenetrable. Normal host defenses may be overwhelmed if large quantities of a virulent uropathogen are introduced into the urinary tract during diagnostic and therapeutic procedures. Iatrogenic bacterial UTI is a common complication of indwelling urinary catheters, especially if an open-ended system is used. Bacterial UTI developed in 20 per cent of healthy adult female dogs after intermittent catheterization, in 33 per cent of male dogs during repeated catheterization, and in 65 per cent of healthy male cats within 3 to 5 days of open indwelling catheterization.[15,31] In a clinical study, infection developed in 52 per cent of dogs and cats with indwelling urinary catheters; risk of infection increased with duration of catheterization.[31] Use of indwelling urinary catheters during diuresis or corticosteroid administration is particularly dangerous. The risk of infection is further compounded if the patient has preexisting urinary tract disease.

Figure 48-5. A closed-system indwelling urinary catheter in a 2-year-old castrated male cat after relief of urethral obstruction resulting from a matrix-crystalline urethral plug.

Iatrogenic bacterial UTIs may be prevented by (1) avoiding indiscriminate use of urinary catheters, (2) using a closed system of collection when indwelling urinary catheters are used (Figure 48-5), (3) being cautious about use of indwelling urinary catheters when patients are undergoing diuresis, (4) avoiding use of indwelling catheters in patients that are immunosuppressed or are receiving immunosuppressive medications such as glucocorticoids, (5) using antimicrobials appropriately with urinary catheterization, and (6) using diagnostic and therapeutic techniques that minimize trauma and microbial contamination of the urinary tract. Although it seems logical to administer antimicrobial agents while an indwelling urinary catheter is inserted in an effort to decrease iatrogenic infection, the practice is discouraged. Concomitant oral or parenteral administration of antimicrobial agents during indwelling urethral catheterization reduces the frequency of developing a bacterial UTI; however, it promotes development of UTI caused by multidrug-resistant bacteria.[31]

Eradication of Underlying Cause(s)

Although antimicrobial agents are the cornerstone of treatment of UTIs, they should be used in a logical fashion. Overuse and misuse of antimicrobial agents may result in emergence of resistant organisms that have implications for veterinary and human health. A bacterial UTI occurs in association with

compromise of host defense mechanisms, which may be transient or permanent. Transient compromise often results in development of a simple or uncomplicated UTI; however, permanent compromise results in development of complicated UTI. Evaluation for, and correction or control of, the compromise(s) in host defense mechanisms are important in treatment of UTI, especially with recurrent UTI.

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Chapter 49

Performing the Neurological Examination*

Joan R. Coates and Jonathan M. Levine

The neurological examination uses a systematic approach by which the clinician elicits a series of reactions and reflexes to assess the functional integrity of the nervous system (Table 49-1). A deficit of a reaction establishes presence of a neurological abnormality, whereas a reflex ascertains the neuroanatomical localization. Additionally, the neurological examination helps determine lesion extent and prognosis.[1-4] Initial steps in this process include a detailed history and thorough physical examination, which add to the validity of the neurological examination. Other ancillary diagnostic procedures are used to exclude metabolic, cardiogenic, or orthopedic disorders that can mimic neurological disease.

Obtaining the proper neuroanatomical localization is crucial to formulation of a differential diagnosis and diagnostic plan. Disease of the upper motor neuron (UMN) develops when an interruption occurs in the descending inhibitory pathways from the UMNs in the brain and spinal cord. Clinical signs of UMN disease are marked by weakness, spasticity, and normal to exaggerated reflexes. Diseases of the lower motor neuron (LMN) affect the cell body, nerve root, and peripheral nerve. Clinical signs of LMN disease include muscle weakness, atrophy, and loss of reflexes.

Some cats are a challenge to examine, and handling requires patience and persistence to complete the examination process. A cat often tolerates only a finite amount of time for the examination process. Less hands-on manipulation usually is best; this makes patient observation a more important component of the neurological examination. Sometimes, the examiner needs to be selective for which components of the neurological examination will be most informative given that the entire examination cannot be completed.

An orderly sequence to the neurological examination is important. Tests that evaluate presence of pain should be left as the last part of the examination process. The cat will be less likely to anticipate a painful stimulus during the rest of the examination. This chapter emphasizes components of the neurological examination and techniques used specifically for evaluating cats.

OBSERVATION

Observation is the first step, and probably the most important, of the neurological examination in cats. When observing how the cat interacts with its environment, abnormalities in mentation, behavior, posture, and gait may be detected.

Mentation

Appropriate mentation requires normal interaction between the ascending reticular activating system (ARAS) and the cerebral cortex.[5] The ARAS is a network of neurons located in the medulla and pons that receives sensory projections and projects to the thalamus and diffusely projects to the cerebral cortex. Physiological or structural pathologies of this pathway can alter mentation. Small parenchymal lesions in the ARAS of the brain stem cause severe disturbances in mentation, whereas focal cerebrocortical lesions tend to have more subtle signs.

A normal cat should be alert and responsive to external stimuli. Descriptions of altered levels of consciousness include obtundation, disorientation, stupor, and coma. A cat that is obtunded (depressed, dull, excessive sleepiness) responds appropriately to its environment but does so only when encouraged. A disoriented patient resists physical restraint, paces, and may show agitation and overreactivity. Stupor is a state in which the cat responds only to painful stimuli. Comatose patients are completely unresponsive, even to noxious stimuli. Classification of consciousness in determination of prognosis can facilitate assessment of disease. A modified Glasgow Coma Scale is a numerical scoring system that evaluates motor and brainstem function and level of consciousness.[6] This scale has been evaluated statistically for use in dogs; however, the scoring system also can be applied to cats.

Abnormal behavioral patterns and mentation are not considered synonymous and can be difficult to differentiate in cats. Aggression, fear, or disinterest is seen commonly in a normal cat that reacts to its new surroundings. Often, client history is a more reliable tool for differentiation between abnormal

*The authors would like to acknowledge Howard Wilson for assistance with the photography.

Table 49-1 | **Components of the Neurological Examination**

Observation*	Mentation	
	Posture	
	Gait	
	Abnormal movements	
Postural reaction testing	Conscious proprioception*	
	Hopping	
	Wheelbarrow	
	Extensor postural thrust	
	Placing	
	Tactile	
Spinal reflexes	**Myotatic**	
	Thoracic limbs	Pelvic limbs
	Biceps	Patellar
	Triceps	Cranial tibial
	Extensor carpi radialis	Gastrocnemius
	Flexor withdrawal*	
	Thoracic limbs	Pelvic limbs
	Cutaneous trunci	
	Perineal reflex	
Cranial nerve evaluation	Visual	
	Menace response*	
	Pupillary light reflex*	
	Pupil size*	
	Physiologic nystagmus*	
	Strabismus	
	Pathological nystagmus	
	Masticatory muscle mass*	
	Palpebral reflex*	
	Facial sensation*	
	Facial muscle symmetry	
	Gag reflex*	
	Tongue movement/symmetry*	
Sensory evaluation	Paresthesia	
	Hypesthesia	
	Hyperesthesia	
	Anesthesia	
	Superficial nociception*	Deep nociception†

*These tests are required components of the neurological examination.
†Perform only if superficial nociception is absent.

behavior and mentation. Behavior probably is best thought of as representing the *quality* of mental alertness.[7] A cat may be bright, alert, and responsive (conscious state) but also aggressive, agitated, or docile (behavioral pattern). The limbic system plays a central role in generation and modulation of behavioral patterns. Structures within the limbic system include the amygdala, septal nuclei, habenular nuclei, hippocampus, cingulate gyrus, and parahippocampal gyrus.[5,8] Emotions such as attention, panic, and fear require significant prefrontal modulation in addition to limbic input.[9-11] Extrapyramidal nuclei that consist of the striatum and several brainstem autonomic structures also contribute to the regulation of behavioral patterns.[9]

Posture

Posture relates position of the head, torso, and limbs with respect to gravity. Abnormal head positions include tilt, headturn (yaw), ventroflexion, and torticollis. A head tilt usually is indicative of asymmetrical vestibular dysfunction and is ipsilateral to the side of the lesion. Head rotation usually is within the horizontal plane; therefore, the ear on the affected side is positioned down. The tilt reflects the side of reduced input from the vestibular apparatus or associated brainstem components, which results in an ipsilateral loss of antigravity muscle tone. Central lesions can cause a head tilt in either direction (see Chapter 56). Cats with vestibular dysfunction also may exhibit torticollis as a result of an ipsilateral decrease in vestibular input. Torticollis refers to a turn or twist of the neck and trunk.

A head turn without a tilt usually is observed with asymmetrical cerebrocortical disease. The head turn, or yaw, usually is ipsilateral to the lesion. The head turn may be a sign of aversion or hemi-inattention to contralateral stimuli.[12,13] A cat with a right cerebrocortical lesion may ignore environmental input from the left side and have a persistent head turn to the right. Visual and motor deficits contralateral to the side of the prosencephalic lesion also may contribute to this postural phenomenon.[12,13]

Ventroflexion of the neck is a common phenomenon in cats and is seen typically with disorders of neuromuscular weakness. Multiple causes exist for ventral neck flexion in cats. Commonly recognized causes include hypokalemia, thiamine deficiency, myasthenia gravis, and other metabolic disorders.[14,15] Abnormal head movements include wide excursions, tremors, and head-bob as observed with dysfunction of the cerebellar and vestibular systems.[16]

A normal cat should stand with limbs spread to shoulder and hip widths. Animals with spinal malformations also can show kyphosis (dorsal deviation), scoliosis (lateral deviation), and lordosis (ventral deviation).[17] Increased or decreased limb tone is associated with abnormal postures. Limb hypotonia and hypertonia reflect LMN and UMN disease, respectively. A wide-based stance occurs with loss of proprioception but is recognized more frequently with vestibular and cerebellar dysfunction. Animals with spinal cord (especially cervical) and peripheral nerve dysfunction also may show a wide-based stance. A posture of an upright position on toes and limbs tucked under the body torso may indicate pain or compensatory mechanism for limb weakness. Plantigrade and palmigrade stance is observed with weakness, more commonly associated with LMN dysfunction. Another nonspecific sign of weakness in cats is the inability to retract their claws passively. Deficits in tail movement also may signify weakness. A non–weight-bearing limb position is observed with orthopedic diseases, but neurogenic-associated lameness is seen with radicular (nerve root) pain.

Specific postural abnormalities can occur in recumbent cats. Opisthotonus is characterized by extension of the neck and rigid extension of the thoracic limbs. This posture often occurs with lesions in the rostral cerebellum, caudal midbrain, or other structures within the caudal fossa. Transection between the rostral and caudal colliculi of the midbrain in cats results in loss of rubrospinal modulation that facilitates the muscles of limb flexion and disinhibition of the vestibulospinal and reticulospinal pathways, causing excessive extensor tone. Excessive extensor tone presumably leads to a opisthotonic posture in cats with midbrain transection.[18] Decerebrate rigidity is characterized by extension of all limbs and opisthotonus.[19] Decerebellate rigidity is manifested by extension of the thoracic limbs, flexion of the pelvic limbs and trunk, and opisthotonus. Rostral cerebellar lesions also cause a release of extensor inhibition.[20] Schiff-Sherrington posture is characterized by increased extensor tone of the thoracic limbs and flaccid paralysis of the pelvic limbs after acute T3-L3 spinal cord lesions. "Border cells," which exert inhibitory influences on extensor motor neurons of the thoracic limbs via the fasciculus proprius, are located predominantly in the L2-L4 spinal cord segments.[21] Damage to

these cells or interruption of the fasciculus proprius as it ascends through the thoracolumbar spinal cord causes release of thoracic limb extensor motor neurons and hypertonia.[22] This phenomenon is most common in dogs but is considered rare in cats because they do not survive the traumatic insult. Similar postures associated with tetanus manifest as muscle rigidity rather than spasticity (see Chapter 8).

Gait

Gait is assessed with regard to coordination, voluntary motor functions, and direction. Cats must be evaluated on a non-slick surface and given plenty of time and space for proper gait assessment. Cats with paresis also show an inability to jump on or off higher objects. The action of gait is characterized by a swing (flexion-type reflex) and stance (extensor-thrust reflex) phase.[23-26] The voluntary system recruits the flexor muscles to initiate the swing phase, and the postural system recruits the extensor muscles for the stance and propulsive phase.[27] Cats with UMN weakness often have a gait with a long stride, whereas the stride length is shortened with LMN weakness.[22] Cats with LMN pelvic limb weakness may have a "bunny hopping" gait.

Lameness is characterized by a shortened stride in the affected limb, accompanied by a longer stride in the contralateral limb.[28] Abnormal gait of orthopedic origin usually manifests a lame gait. Lameness also can be of neurogenic origin such as with radicular pain (nerve root signature). Ataxia is defined as lack of coordination without paresis, spasticity, or other involuntary movements. Ataxia is observed with vestibular, cerebellar, and sensory or proprioceptive dysfunction. Cerebellar ataxia often is characterized by dysmetria, which denotes stride movements that are too short (hypometria) or too long (hypermetria).[29] Vestibular ataxia is observed with other signs of vestibular dysfunction. A patient with bilateral vestibular disease exhibits a crouched posture with wide head excursions.

The degree of loss of voluntary motor movement is described as paresis or plegia. *Paresis* is a partial voluntary motor deficit or weakness, whereas *plegia* denotes complete loss of voluntary movement. More descriptive terms are used depending on the extent of limb involvement: *tetraparesis/plegia* when all limbs are affected; *paraparesis/plegia* when the pelvic limbs are affected; *monoparesis/plegia* with one limb affected; and *hemiparesis/plegia* with ipsilateral thoracic and pelvic limb involvement.

Cats with asymmetrical disease commonly manifest circling or leaning. Tight circles usually suggest vestibular dysfunction, whereas wide circles or a lean in one direction suggests cerebrocortical dysfunction. Furthermore, gait with cerebrocortical dysfunction often is normal but may lack purposeful action. Gait from brainstem or spinal cord dysfunction often manifests with more evidence of paresis.

CRANIAL NERVE EVALUATION

Examination of the cranial nerves (CN) is useful for localization of an intracranial lesion and presence of peripheral neuropathy. Vision (CN II) is assessed by client history and observing the cat's ability to navigate the exam room or a maze. Visual tracking is evaluated by tossing a cotton ball to the side or in front of the cat. Vision also is tested specifically using the menace response (Figure 49-1) to evaluate the sensory (CN II) and motor responses (contralateral visual cortex, CN VII, cerebellum). Pupil size is assessed for symmetry and size in the light and dark. The pupillary light reflex (PLR) (Figure 49-2) is useful for localizing a prechiasmal lesion, because the afferent limb is shared by CN II and the efferent limb is supplied by the parasympathetic branch of CN III. A bright light source is used to elicit a direct pupillary muscle constriction and a simultaneous constriction of the opposite eye (consensual reflex). A modification of the PLR is the swinging flashlight test that assesses the direct and consensual PLRs simultaneously as a light source is swung from eye to eye. Flashing a bright light into the eyes and eliciting a blink reflex also induces the dazzle reflex. Although the neuroanatomy of this reflex is not well understood, the efferent pathway is mediated by CN VII.[30] Maximal sympathetic tone is assessed by dark-adapting the

Figure 49-1. The menace response is elicited by making a sudden gesture with a hand or finger and watching for a behavioral response and blink reflex. No air currents should be created because this also stimulates the ophthalmic branch of CN V.

Figure 49-2. The pupillary light reflex (PLR) is evaluated by using a bright light source directed from a temporal to nasal position and observing for direct and consensual pupillary constriction. Typically, the pupil ipsilateral of the light source is slightly more constricted. It is ideal to dark-adapt the eyes before performing the PLR.

Figure 49-3. Physiological nystagmus (oculocephalic reflex, doll's eye reflex) is elicited by turning the head in a horizontal **(A)** and vertical plane **(B).** The slow phase of eye movement is away from, and the fast phase is toward, the direction of the head turn. Another method for eliciting physiological nystagmus is to support the cat in an elevated position at arms length, and to move from side to side in a semicircle while observing for the slow and fast saccades **(C)**.

patient before performing the PLRs. The PLR may be impaired and difficult to assess in cats with high resting sympathetic tone. A Horner's syndrome (miosis, enophthalmos, third eyelid protrusion, and ptosis) may be manifested with ipsilateral sympathetic nerve dysfunction (see Figure 38-6, *A*). The sympathetic pathway consists of first (hypothalamus to T1-T3), second (T1-T3 to cranial cervical ganglion), and third-order (cranial cervical ganglion to pupillary dilator muscle) neurons. A lesion anywhere along this pathway has potential to cause Horner's syndrome.

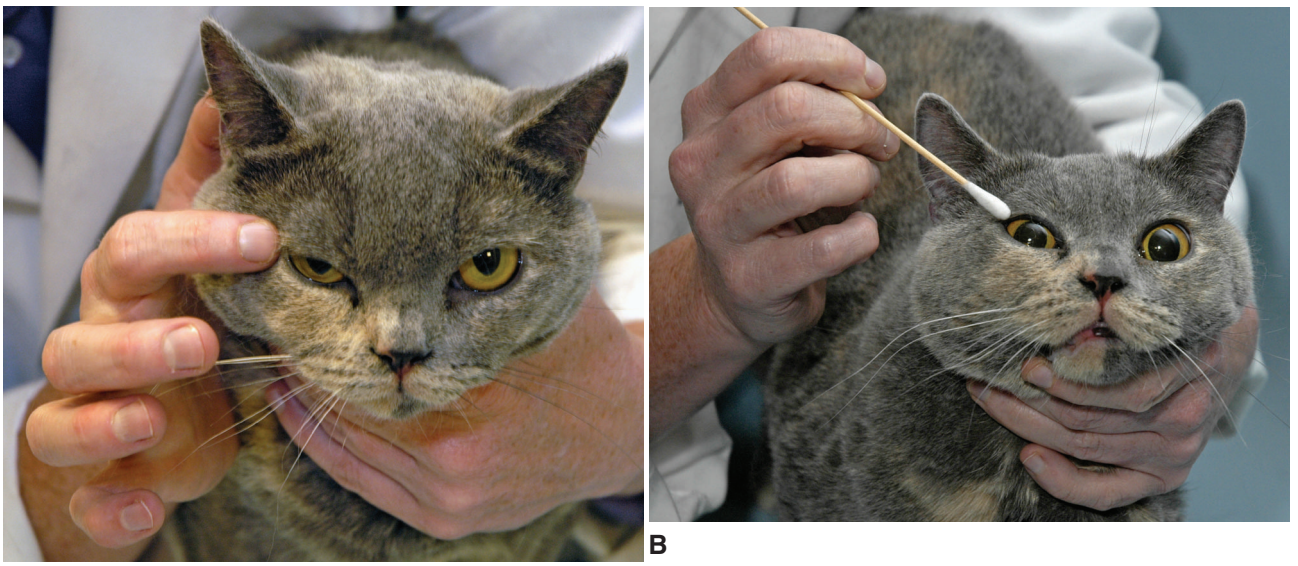
Eye position and movement are mediated by CNs III, IV, and VI through the sensory influence of CN VIII as head position changes. Nystagmus is the alternating fast and slow phase of eye movement. The slow phase is opposite to the direction of head movement, and the reflex fast phase is the same direction of the head movement. Physiological nystagmus (oculocephalic reflex, doll's eye reflex) is elicited by horizontal (Figure 49-3, *A*) and vertical (Figure 49-3, *B*) movements of the head and observing the eyes for conjugate movement. Another way to evaluate for physiological nystagmus is to lift

Figure 49-4. Presence of positionally induced strabismus and nystagmus (jerk nystagmus) is detected by rapidly elevating the head or flipping the cat on its back.

Figure 49-5. Careful attention is paid to asymmetry of the facial muscles and vibrissae. Facial symmetry and strength can be assessed further by evaluating the commissure of the buccal mucosa.

and hold the cat at arm's length with the face toward the evaluator and move the patient in a semicircle from side to side (Figure 49-3, *C*). Pathological nystagmus (jerk nystagmus) can be spontaneous (at rest) or induced with a change in head position. Jerk nystagmus consists of a slow phase that is followed by a fast phase. The fast phase of nystagmus is noted and recorded as rotary, horizontal, and vertical. A reliable technique to elicit a pathological nystagmus is to decompensate the cat by flipping it back rapidly (Figure 49-4). Bilateral or unilateral strabismus also may occur at rest or may be induced with a change in head position. Congenital nystagmus (pendular nystagmus) and strabismus occur in some breeds of exotic cats as a result of an anomaly in routing of the visual pathway from the retina to the contralateral visual cortex but cause no visual impairment. Pendular nystagmus also can be a feature of cerebellar dysfunction.

The head is evaluated further for symmetry by palpation for atrophy of the muscles of mastication, namely the temporalis and masseter muscles (mandibular branch of CN V). Muscles of facial expression, ear symmetry, and size of palpebral fissure and commissures of the buccal mucosa (Figure 49-5) assess the motor branches of CN VII. Cats with weakness of the muscles of facial expression also show loss of ipsilateral vibrissae extension. Sensory evaluation of the head assesses the distribution of the sensory branches of CN V (ophthalmic, maxillary, and mandibular).[31] The palpebral reflex (Figure 49-6, *A*)



A **B**

Figure 49-6. Facial sensation (CN V) is assessed by the palpebral reflex, corneal reflex, and stimulation of the vibrissae. **A,** The palpebral reflex is elicited by touching the medial and lateral canthi and observing for a blink reflex. **B,** The corneal reflex is assessed by applying a cotton-tip applicator to the dorsal surface of the cornea and watching for a reflex retraction of the globe (CN VI), protrusion of the third eyelid, and blink (CN VII).

Continued

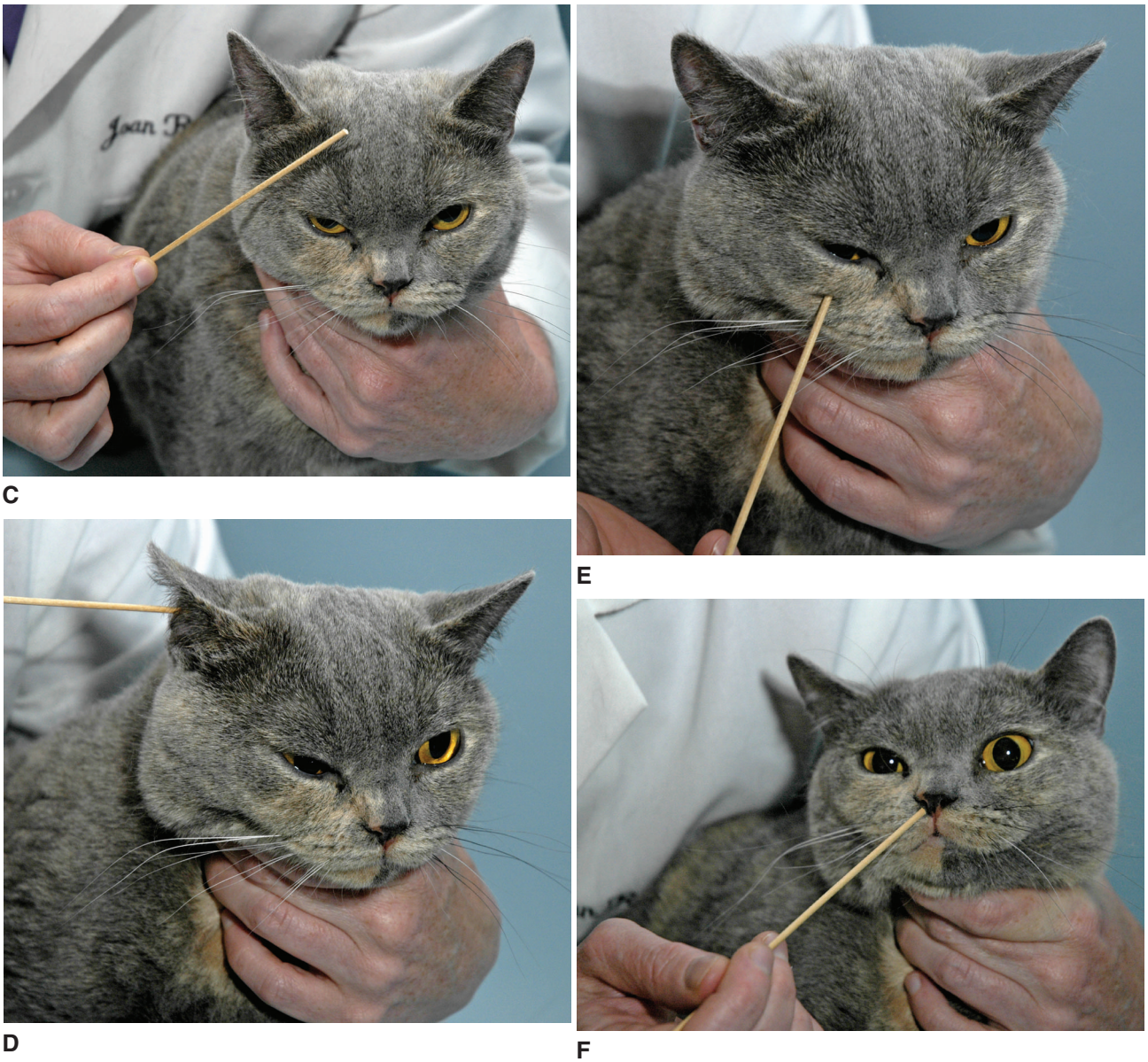


Figure 49-6.—cont'd. Vibrissae around the eyelids **(C),** ears (sensory branch of CN VII) **(D)**, and maxilla **(E)** are stimulated gently to create a behavioral response and reflexive retraction of the vibrissae and facial muscles (CN VII). The planum nasale **(F)** is a particularly sensitive area. The tip of the nose is touched to elicit a behavioral response, retraction of the facial muscles, an eye blink, which is the *trigeminal-facial nerve reflex*, and symmetrical lick of the tongue.

assesses sensory portions of CN V (ophthalmic branch: medial canthus; maxillary branch: lateral canthus) and motor portions of CN VII. Likewise, the corneal reflex (sensory: ophthalmic branch) (Figure 49-6, *B*) also causes caudal retraction of the globe. The vibrissae around the eyelids, ears, and muzzle in cats are very sensitive to touch so facial twitches and an eye blink should be elicited easily (Figures 49-6, *C* through *E*). Stimulation of the planum nasale (Figure 49-6, *F*) assesses the maxillary portion of CN V and a behavioral response is elicited. The tip of the nose is touched to cause a behavioral response, and simultaneous retraction of the facial muscles and eye blink, *trigeminal-facial nerve reflex,*[1] and symmetrical lick movements of the tongue. The mandibular region is less sensitive to touch. Cranial nerves IX and X are assessed during pharyngeal examination by the swallowing reflex (Figure 49-7). Most of the time, palpation of the laryngeal region externally avoids risk of a bite injury. CN XII is assessed during the oropharyngeal examination (Figure 49-8) by evaluating for tongue symmetry and movement during a lick response. Ipsilateral tongue deficits are evident by atrophy and abnormal protrusion and movement.

POSTURAL REACTION TESTING

The purpose of postural reaction testing is to detect subtle deficits in limb strength and coordination.[32] The nervous and musculoskeletal systems must be functional for appropriate completion of these reactions. Poor initiation suggests a

Figure 49-7. The gag reflex is elicited by external palpation of the larynx or stimulating the caudal pharyngeal region during examination of the oral cavity.

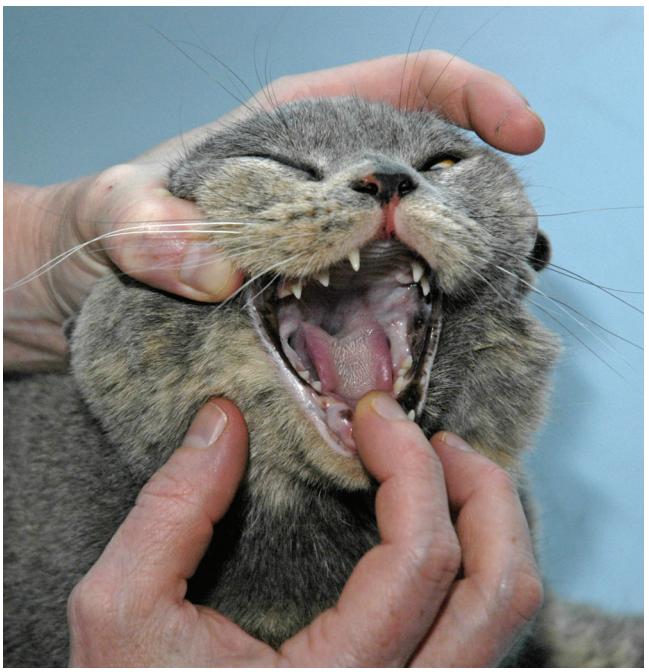


Figure 49-8. When possible, the jaw is opened to assess for strength/tone and visualization of tongue symmetry.

sensory deficit (proprioceptive), whereas poor follow-through suggests motor deficits (paresis). Postural reaction testing should not be attempted in suspected cases of spinal injury.

Paresis also may be accompanied by changes in muscle tone elicited by passive range of movements. Flaccidity indicates absence of muscle tone. Spasticity consists of a selective

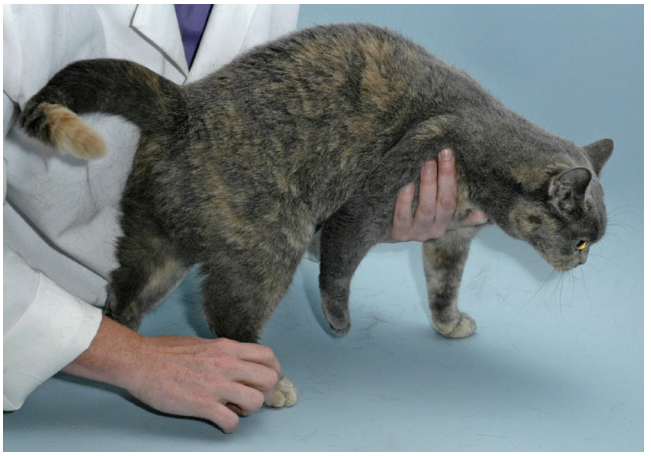


Figure 49-9. Conscious proprioceptive testing is assessed by immediate return of the paw after placement on its dorsum. Cats normally should resist any manipulation of the distal limb.

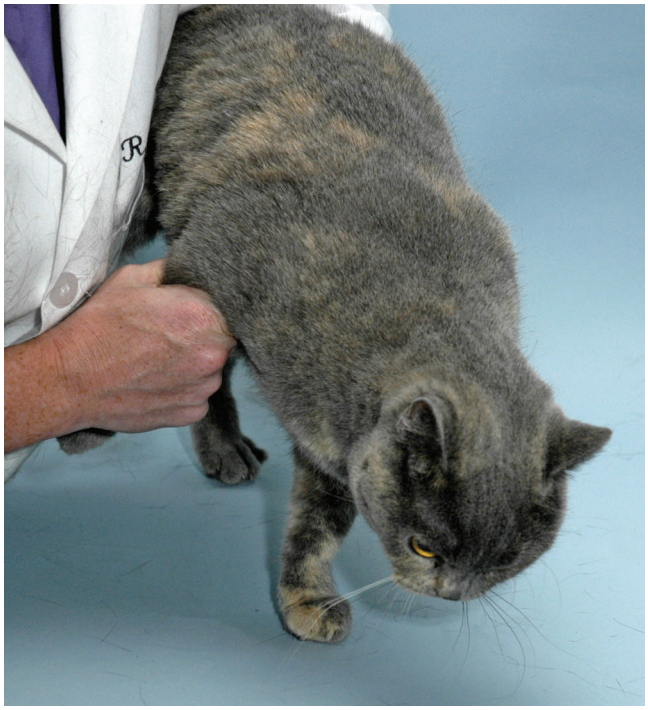
increase in extensor muscle tone. Rigidity is an increase of flexor and extensor tone.

Conscious proprioception (Figure 49-9) is a non–weight-bearing test used to distinguish between orthopedic and neurological disease and evaluates the ability to sense changes in limb position. It is a sensitive but nonspecific test for detecting evidence of neurological disease. Conscious proprioceptive testing usually is normal with orthopedic disease. The test is performed by placement of the dorsal aspect of the paw in contact with the floor. A normal response is a quick replacement of the paw to its palmigrade or plantigrade position. Care is taken to support the patient's weight beneath the truncal area being evaluated. Cats are particularly sensitive to paw touch and normally resist manipulation. The ability of the evaluator to place the paw on its dorsum actually may indicate a proprioceptive deficit in cats. Subtle paresis may become more apparent during testing of other postural reactions.

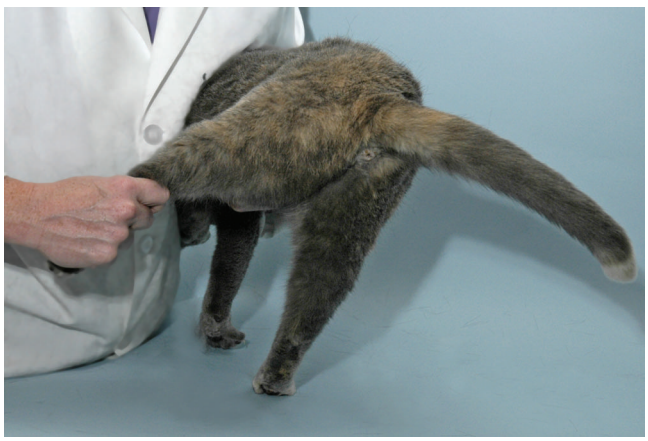
The *hopping* reaction assesses each thoracic (Figure 49-10, *A*) and pelvic limb individually (Figure 49-10, *B*) to accommodate for displacement from its center of gravity. Generally, weight is placed on one limb and the body is shifted in a forward or lateral direction. The limb should reposition itself easily. Particularly in cats, use of minimal restraint and a brisk manner to perform the reaction are important. Cats may choose not to follow through with this reaction voluntarily.

The *placing* reaction is useful in small patients such as cats. Tactile placing is performed by covering the eyes or extending the head and neck as the cat is brought to the edge of a table (Figure 49-11, *A*). The cat should place the paw when the dorsum of the paw touches the edge of a table. The test is repeated using visual placing with the eyes uncovered (Figure 49-11, *B*). The cat should preempt placement of the paws as it approaches the table.

The *wheelbarrow* reaction (Figure 49-12) evaluates thoracic limb function. The abdomen is supported while the pelvic limbs are elevated and the body is pushed forward. Simultaneous elevation of the head to remove visual compensation may accentuate any neurological deficits. Extensor tone in the thoracic limbs also increases as the head and neck are extended (tonic-

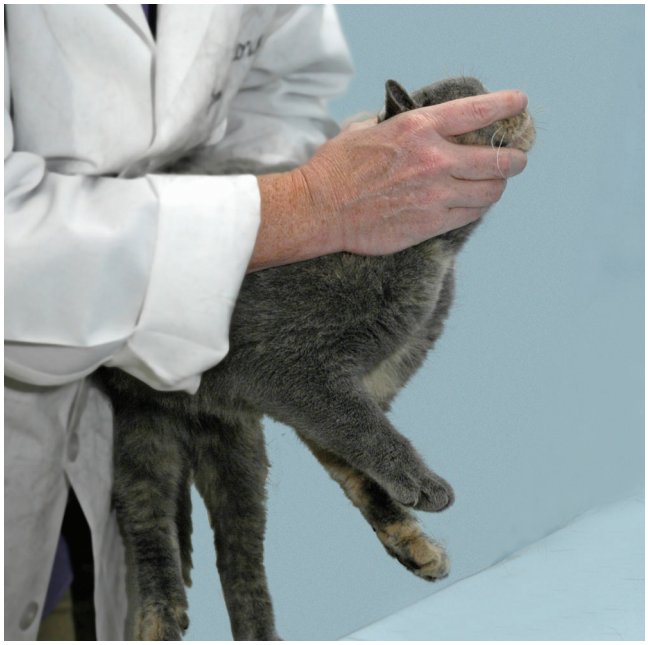


A

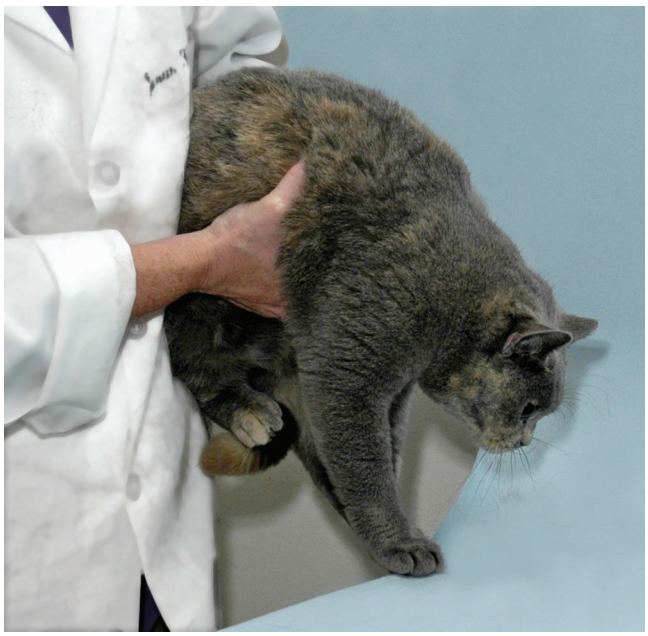


B

Figure 49-10. Hopping response of the thoracic **(A)** and pelvic **(B)** limbs is evaluated by supporting the cat on one limb and displacing its center of gravity in a lateral or forward direction and observing for an immediate compensatory placement response. Each limb is tested individually.



A



B

Figure 49-11. Placing tests are practical in small patients, especially cats. Tactile placement **(A)** is performed first. The eyes are covered or the neck is elevated and the cat is moved toward the edge of a table. As the edge of the table is touched, immediate forward placement of the limb should occur. Visual placement **(B)** is performed similarly. The normal response is an attempt to place the paw before contact with the table.

neck reaction).[22] Thoracic limb strength and symmetry are assessed.

The *extensor postural thrust* reaction (Figure 49-13) evaluates pelvic limb function and strength. The animal is supported by the thorax, and the pelvic limbs are lowered toward the floor. The extensor thrust reflex is manifested by increased pelvic limb extensor tone and spreading of the toes. As the limbs touch the floor, the animal should take a couple of steps backwards. Pelvic limb strength and symmetrical coordination are assessed. Pelvic limb extension is under the influence of the vestibular system. Cats with vestibular dysfunction exhibit ipsilateral loss of extensor tone to the head and neck and to the thoracic and pelvic limbs ("archer posture").[12]

SPINAL REFLEXES (MYOTATIC, FLEXOR WITHDRAWAL, CUTANEOUS TRUNCI)

Spinal reflexes assist with neuroanatomical localization of a spinal cord lesion. A lesion within the UMN pathways causes clonus, exaggerated or normal reflexes, and evidence of paresis or paralysis. LMN lesions are accompanied by a decrease or an absence of spinal reflexes along with signs of paresis or paral-

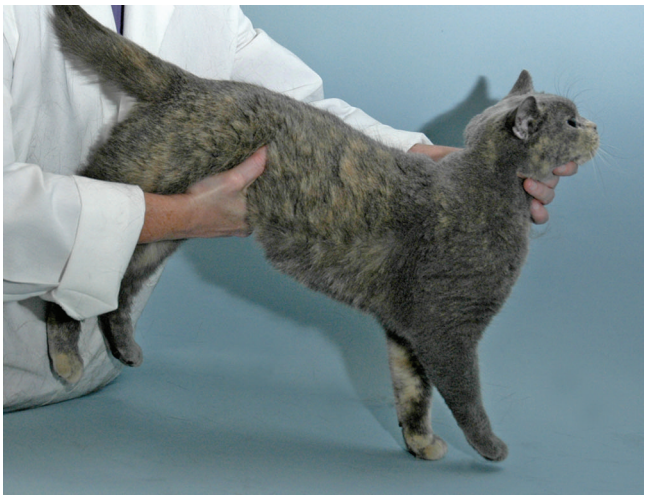


Figure 49-12. Wheelbarrow reaction consists of supporting the caudal torso and moving the cat in a forward direction. The thoracic limbs should gait in a symmetrical fashion. This test is performed with and without the neck extended. Extension of the neck also elicits the tonic neck reflex with increased thoracic limb extension.

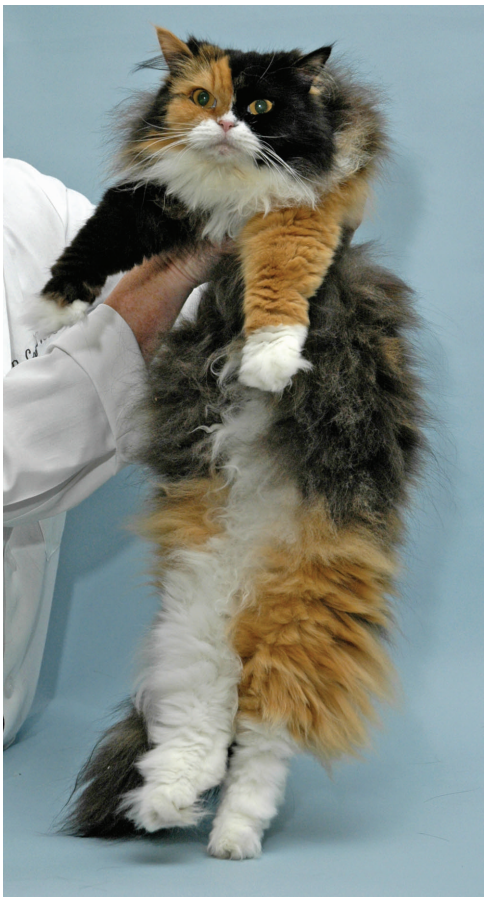
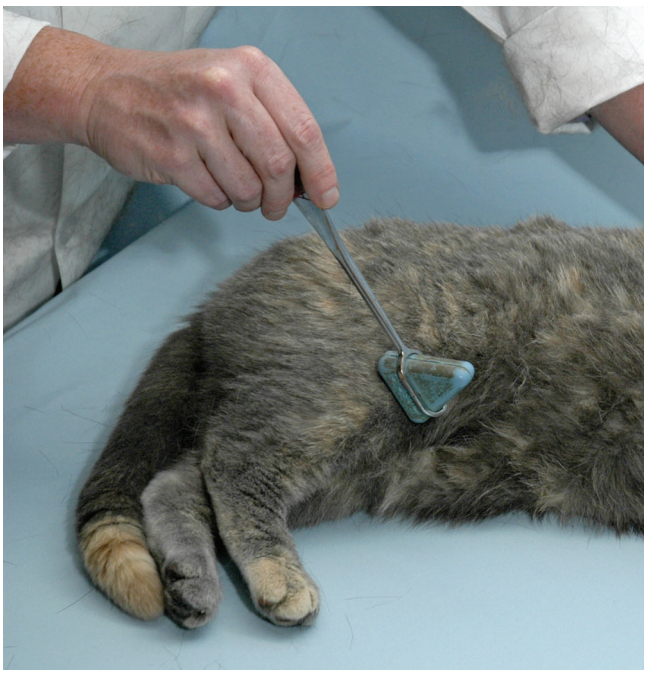


Figure 49-13. Extensor postural thrust involves supporting the cat upright beneath the axillae so that the weight is directed toward the pelvic limbs; the cat should extend the pelvic limbs reflexively and spread the digits in anticipation of touching the floor, and then take backward steps while supporting weight on the limbs. These steps should be symmetrical with good strength and coordination.

ysis. Based on decrease or absence of a spinal reflex involving the thoracic and pelvic limbs, spinal cord segments can be separated into regions for determination of lesion localization: cranial to C5, C6 to T2, T3 to L3, and L4 caudally.

Myotatic reflex or stretch reflex occurs when a stimulus initiates a stretch and contraction of the muscle spindles. Myotatic reflexes also are referred to as monosynaptic reflexes because of a direct synapse of the afferent fibers with the motor neurons of a particular group. It is ideal to palpate and relax the limb for tone using passive range-of-motion; often in cats this is not possible. The patellar reflex (femoral nerve) (Figure 49-14, *A*) is the easiest myotatic reflex to elicit, and the most reliable. Other myotatic reflexes evaluated in animals include gastrocnemius (tibial branch of ischiatic nerve), cranial tibial (Figure 49-14, *B*) (peroneal branch of ischiatic nerve), extensor carpi radialis (Figure 49-14, *C*) (radial nerve), triceps (Figure 49-14, *D*) (radial nerve), and biceps (Figure 49-14, *E*) (musculocutaneous nerve). Reflex evaluations should be interpreted as clonus, exaggerated, present, decreased, or absent. Reflexes may be interpreted as exaggerated in normal cats that are excited or anxious. Clonus occurs with UMN disease and is a repetitive contraction of a muscle or muscle group.

The *withdrawal reflex* is polysynaptic reflex that occurs in response to a noxious stimulus. The flexor withdrawal reflex is performed with the cat in lateral recumbency and a noxious stimulus is applied to the skin of the toes. The flexor withdrawal reflex of the thoracic limb (Figure 49-15, *A*) is observed for flexion of the carpal (median and ulnar nerves) and elbow (musculocutaneous nerve) joints. The flexor withdrawal reflex of the pelvic limb (Figure 49-15, *B*) is observed for stifle and hock (ischiatic nerve) flexion. In cats that resist restraint, the withdrawal reflex is considered the most important spinal



A

Figure 49-14. The myotatic reflexes usually are performed using a pleximeter with the patient in lateral recumbency. The patellar reflex **(A)** is elicited by percussion of the patellar tendon and observation for contraction of the quadriceps muscle and extension of the stifle.

Continued

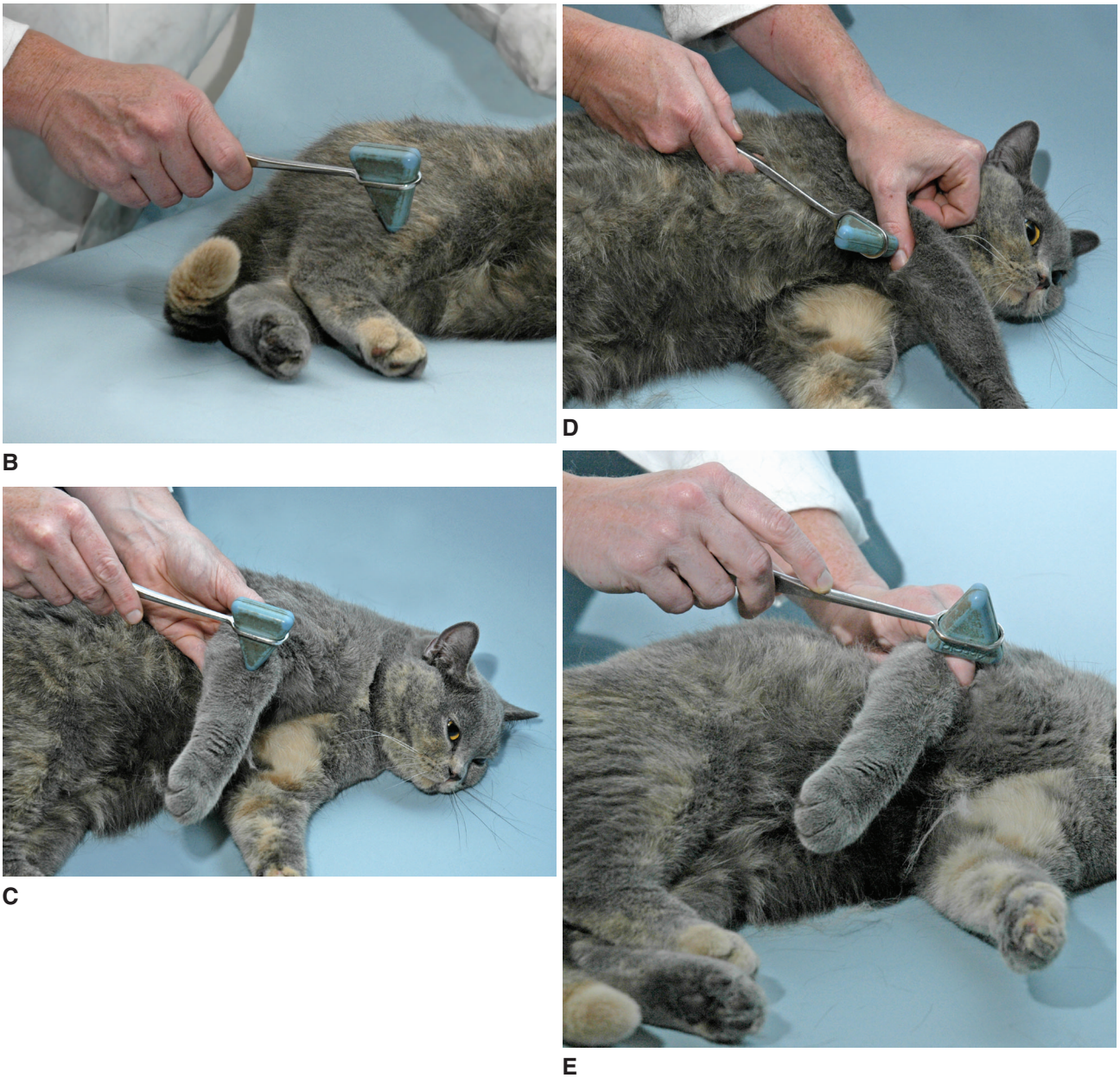


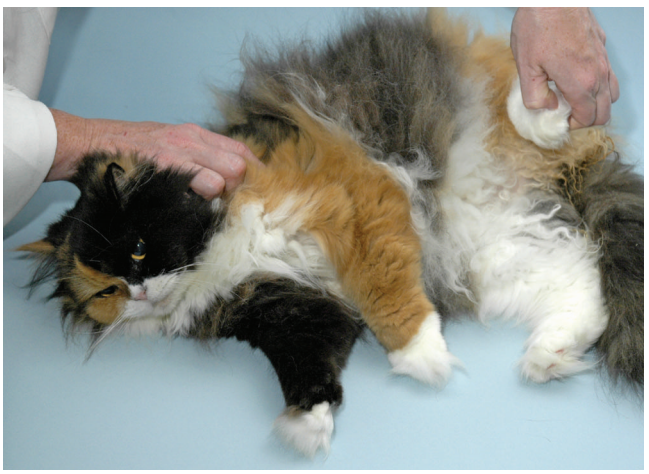
Figure 49-14.—cont'd. The cranial tibial reflex **(B)** is elicited by percussion of the proximal cranial tibialis muscle and observation for flexion of the hock. The extensor carpi radialis reflex **(C)** is elicited by percussing its proximal muscle belly and observing for extension of the carpus. The triceps reflex **(D)** is elicited by extension of the shoulder cranially, isolation of the tendon of the triceps muscle with a finger near its insertion on the olecranon of the ulna, and direct percussion over the finger. The biceps reflex **(E)** is elicited by extension of the shoulder caudally, isolation of the tendon of the biceps brachii and brachialis muscles near their insertion on the cranial and proximal surfaces of the radius, and direct percussion over the finger. Elbow flexion and movement of the muscle bellies are observed.

reflex to assess and easiest to elicit. An alternative way to assess withdrawal reflexes is to support the cat by the thorax and pinch each paw individually. A brisk withdrawal of the limb should be observed.

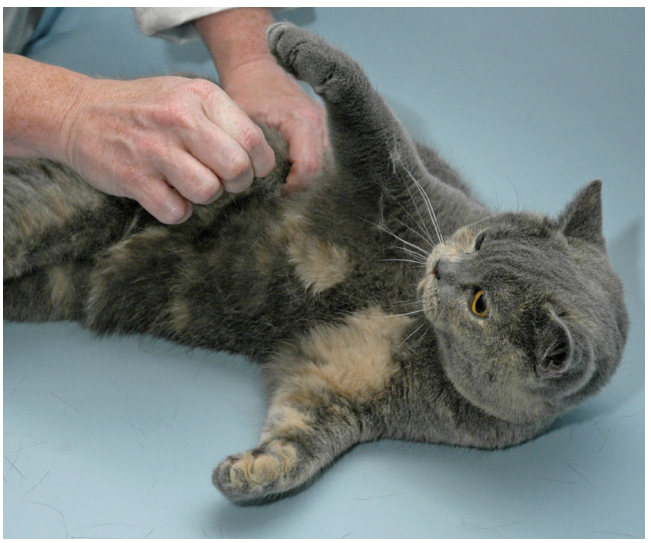
During performance of the flexor withdrawal reflex, the evaluation also observes for presence of a crossed extensor reflex. As the flexor reflex is elicited by a noxious stimulus, the opposite limb will have a reflex extension. The crossed extensor reflex serves as a protective mechanism to maintain posture in a standing animal. When a noxious stimulus is applied, a series of reflexes cause ipsilateral limb flexion and withdrawal, and contralateral limb extension (crossed extensor reflex).[24] The crossed extensor reflex is inhibited normally when laterally recumbent. A crossed extensor reflex may be elicited with UMN disease cranial to the L4 spinal cord segment as a consequence of loss of descending inhibitory UMN pathways to the contralateral motor neurons. Presence of the reflex has not been useful in determining prognosis.[22]

The *cutaneous trunci* reflex (Figure 49-16) has an extensive reflex arc by which the afferent limb is segmental. The reflex is first detected at the level of the fifth lumbar vertebrae. Sensory branches originate from the cutaneous thoracic nerves

A



B



C

Figure 49-15. The flexor withdrawal reflexes are performed by pinching the digits of the thoracic limbs **(A)** while observing for flexion of the elbow and carpal joints, and pelvic limbs **(B)** while observing for flexion of the hock and stifle joints. Superficial nociception is assessed simultaneously by observing for a behavioral response **(C).** If no behavioral response is elicited, deep nociception is tested by clamping the digits with a hemostat.

Figure 49-16. The cutaneous trunci reflex is assessed by pinching the skin beginning lateral to the dorsal spinous processes and cranial to the wing of the ilium. A skin twitch and behavioral response are observed. Because the sensory component of this reflex is segmental, the test is repeated from caudal to cranial until a reflex is elicited.

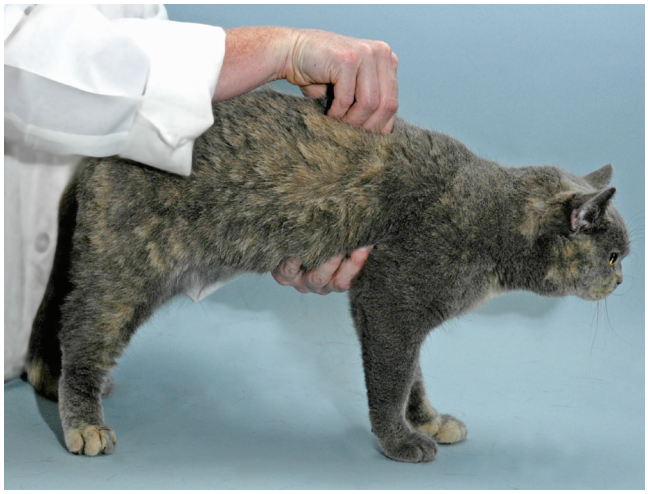
and ascend the spinal cord bilaterally to synapse with the motor neurons of the lateral thoracic nerve (C8, T1 segments) that innervates the cutaneous trunci muscle.[22] A skin twitch is observed bilaterally, stronger on the ipsilateral side. An UMN thoracolumbar lesion would cause an absent response caudal to the level of a lesion that disrupts the superficial pain pathway.[1] This test sometimes is difficult to elicit reliably in cats.

The *perineal reflex* assesses the sacral nerves 1, 2, and 3, which include the pudendal nerve. A skin pinch of the anus is used to elicit contraction of the anal sphincter and ventral flexion of the tail. The anus is visualized for symmetry and tone. The sacral nerves also contribute to the pathways affecting fecal and urinary continence. Pathology of the sacral nerves often affects the coccygeal nerve roots simultaneously.[33] In particular, a limp tail and paralysis should provide initial suspicion of coccygeal nerve damage.[34]

SENSORY EVALUATION (HYPERESTHESIA, SUPERFICIAL/DEEP PAIN NOCICEPTION)

Testing of tactile sensation assesses the cat's behavioral response to noxious and nonnoxious stimuli. These are classified according to degree of sensitivity: *anesthesia* (absence of a conscious response to a noxious stimulus); *hypesthesia* (decrease response to a stimulus); *paresthesia* (pain elicited without any external stimuli); and *hyperesthesia* (pain induced using an innocuous stimulus).[35] Sensory abnormalities assist with localization and prognostic assessments.

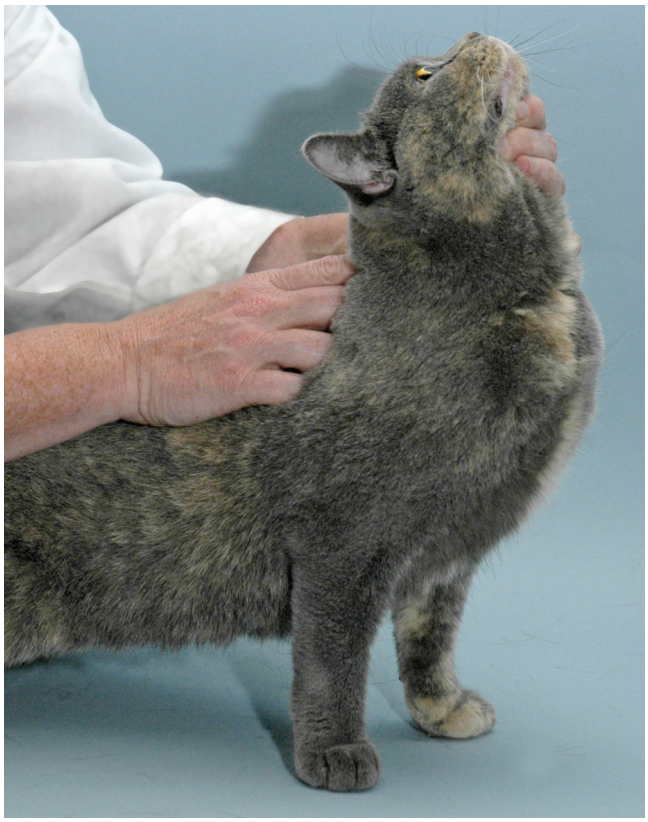
Hyperesthesia is a useful localizing sign to denote an increased sensitivity to a nonnoxious stimulus such as deep palpation of the spinal column, cranium, and limbs. Evaluation is performed beginning distal to the area of lesion suspicion and directed proximally to the area of lesion suspicion. Support is applied beneath the truncal area being evaluated (Figure 49-17, *A*). Specifically, supporting the pelvis during palpation of the lumbosacral joint is important to isolate it from hip manipulation (Figure 49-17, *B*). Applying tail traction by dorsal and lateral flexion is a sensitive technique for determining presence of hyperesthesia in the lumbosacral region. Dorsiflexion



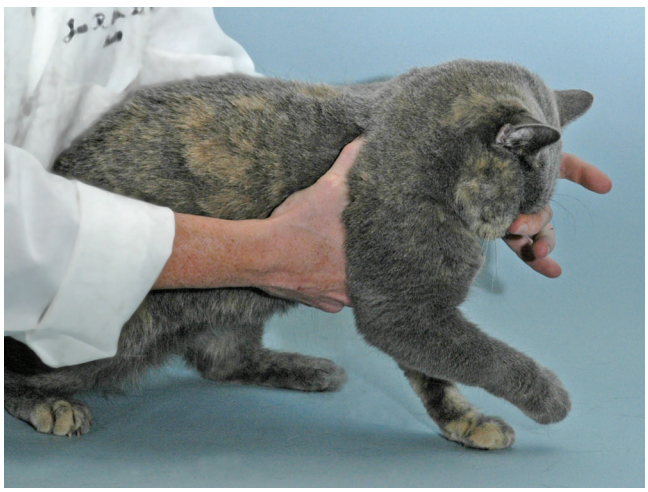
A

B

Figure 49-17. A, Paraspinal hyperesthesia is assessed by palpation of the paraspinal muscles, and applied from a distal to proximal direction of the area of lesion suspicion using varying degrees of pressure. Presence of muscle fasciculations with a behavioral response is suggestive of hyperesthesia. The truncal region is supported beneath the area of palpation. Firm pressure is used to palpate the paraspinal muscles dorsally and laterally to each dorsal spinous process. **B,** The lumbosacral *(L-S)* interarcuate space is palpated specifically with the hip in extension and applying pressure midline at the level of the ilial crest. Tail extension and flexion also may elicit pain in a disease state by traction of the nerve roots.



A



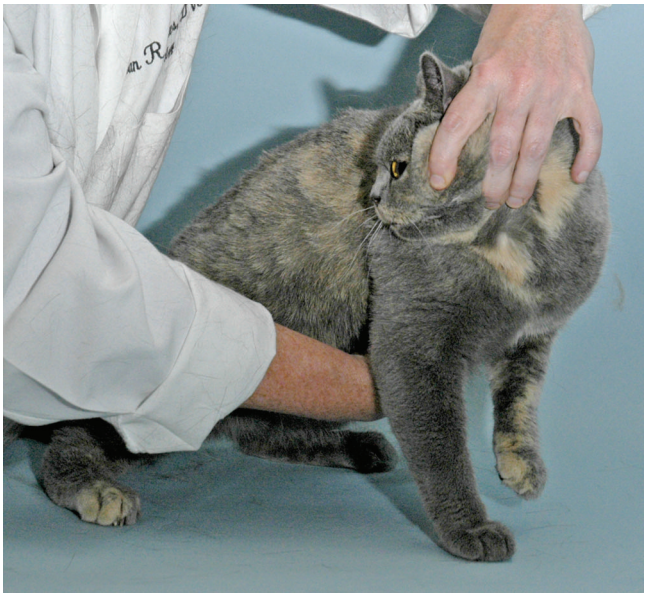
B

Figure 49-18. Manipulation of the neck is a sensitive method for eliciting cervical spinal hyperesthesia. The neck is placed in extended **(A),** flexed **(B).**

(extension), ventroflexion, and lateral flexion (Figure 49-18, *A* through *C*) of the neck assist with ascertaining hyperesthesia within the cervical spine. Upon lateral flexion, the range-of-motion for the neck should extend to the torso. Paraspinal hyperesthesia, especially of the thoracolumbar region, can be difficult to assess in cats because of an increased sensitivity to palpation. This evaluation may need to be repeated at different times to obtain a consistent response. Hyperesthesia is considered a useful localizing sign. Anatomical structures that are pain-sensitive include the meninges, nerve roots, intervertebral discs, joints, bones, and muscles. Inflammatory and compressive spinal disorders are likely differential diagnoses for patients with paraspinal hyperesthesia (see Chapter 51).

Superficial nociception is evaluated during cutaneous testing using a skin pinch. The sensory branch of individual nerves is assessed further by mapping their dermatomal distribution. The autonomous zone is the region of skin innervated by one nerve root.[36-38] Superficial nociception of the limbs is perceived by the examiner as a behavioral response while performing the withdrawal reflex (see Figure 49-15, *C*). These spinal pathways are shared with proprioception, touch, and temperature modalities, and ascend bilaterally. If a superficial pain response is not elicited, deep pain perception is then assessed.

Deep nociception is elicited from small unmyelinated fibers within the periosteum. This is evaluated by placing hemostats across the digits and observing for a behavioral response. Most importantly, a withdrawal reflex of the limbs by itself is *not* an indicator for the cat to perceive deep pain. Deep pain pathways are bilateral and are located deep within the spinal cord white



C

Figure 49-18.—cont'd. Lateral flexed **(C)** positions. Movement is observed for resistance, range of motion, and behavioral response to pain.

matter.[22] Loss of deep nociception is considered a poor prognostic sign. This test is particularly important to evaluate in cats that have developed "spinal-walking" as a sequela to severe spinal cord injury[23,24,39] (see Chapter 51). These cats *appear* to have a voluntary ability to ambulate but fail to have perception of noxious stimuli. Loss of deep nociception often is associated with severe spinal cord injury and indicates a guarded to poor prognosis for return of voluntary limb function.

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Chapter 50

POLYNEUROPATHIES

Karen Dyer-Inzana

The peripheral nervous system is a vital portion of the nervous system. Peripheral neuropathies can affect motor, sensory, and autonomic nerves and their supporting structures. Clinical signs vary with the specific disease process and component of the motor unit affected. Motor neuropathies cause weakness, hyporeflexia, and rapid muscle atrophy. Weakness in cats often is manifested as reluctance to move, plantigrade stance (Figure 50-1), and ventroflexion of the head and neck (Figure 50-2). With pure sensory neuropathies, muscle mass and strength usually are preserved but marked ataxia and poor coordination are present. Spinal reflexes may be abolished by both pure sensory neuropathies and motor neuropathies. Involvement of the autonomic system results in a myriad of signs attributable to loss of parasympathetic and/or sympathetic function. Abnormal pupil size and function, decreased salivation, lacrimation, dysuria, and bowel stasis are common. Trauma can result in injury to isolated segments of the motor unit but often affects two or more components.

Clinical suspicion of a peripheral neuropathy can be confirmed with electrodiagnostic evaluation in addition to nerve and muscle biopsy. Detailed descriptions of each of these techniques have been well described in the veterinary literature.[1,2] Once the diagnosis of polyneuropathy has been made, the search begins for the underlying cause and potential treatments. This review describes a wide range of recognized causes for peripheral nerve disease in cats.

INHERITED AND CONGENITAL NEUROPATHIES

Neuropathy in Birman Cats

Reports of four Birman cats describe a plantigrade gait, posterior ataxia, and slight hypermetria in all limbs between 8 and 10 weeks of age.[3] The clinical course is progressive. Light microscopic examination of the central nervous system (CNS) reveals diffuse loss of myelinated fibers in the cerebral and cerebellar white matter, and terminal ends of the fasciculus gracilis and lateral pyramidal tracts. In the peripheral nervous system is loss of myelinated fibers in the distal portion of the sciatic nerves. Based on lesion distribution, this was classified as a central-peripheral distal axonopathy, which was suspected to be inherited.

Hyperchylomicronemia

Many breeds of cats (domestic short-haired [DSH], Himalayan, Persian, Siamese) from several different countries (United States, New Zealand, United Kingdom, Europe) have been described with a disorder in lipoprotein metabolism.[4-7] Affected cats have a fasting hyperchylomicronemia and hypertriglyceridemia. Lipid granulomas (xanthomata) develop in multiple organs including liver, spleen, kidneys, lymph nodes, and heart. Clinical signs of neuropathy are secondary to lipid deposition and peripheral nerve compression in areas of pressure points and where nerves exit foramina. Common nerves predisposed to compressive neuropathy include the sympathetic related to Horner's syndrome, tibial, and radial nerves. Hyperchylomicronemia is caused by mutation of the lipoprotein lipase gene and subsequent deficiency of lipoprotein lipase enzyme activity, a crucial enzyme in the regulation of lipoprotein and lipid metabolism.[8,9] These affected cats serve as an important animal model for human lipoprotein lipase deficiency and gene therapy.[10]

Hyperoxaluria (L-Glyceric Aciduria) in Domestic Short-Haired Cats

Cats from a single breeding colony with a condition analogous to primary hyperoxaluria type 2 in human beings have been reported.[11,12] Affected cats develop acute renal failure between 5 and 9 months of age as a sequela to deposition of calcium oxalate in the kidneys. Many of these cats also exhibited generalized muscle weakness, depressed spinal reflexes, and diminished pain perception. Serum biochemistry reveals

Figure 50-1. Diabetic cat with generalized peripheral neuropathy. Note the plantigrade stance.

Figure 50-2. Domestic short-haired cat exhibiting cervical spinal ventroflexion characteristic of neuromuscular weakness.

changes compatible with primary renal failure. Increased concentrations of oxalate and L-glycerate have been measured in urine. Less than 5 per cent of the normal enzyme activity of D-glycerate dehydrogenase was detected in livers of affected cats. Light microscopy of peripheral nerves showed evidence of Wallerian degeneration. Axonal swellings containing accumulations of neurofilaments are present in the proximal axons of spinal ventral horn cells, ventral roots, intramuscular nerves, and dorsal root ganglia. Oxalate crystals are not observed in tissues other than the kidneys. The metabolic defect is believed to be inherited as an autosomal recessive trait, but the pathogenesis of the peripheral nerve degeneration remains unclear. A motor neuropathy has been observed in human patients with hyperoxaluria type 1 but axonal swelling was not apparent.

Neimann-Pick Disease in Siamese Cats

Sphingomyelin lipidosis is an inherited defect that results in the visceral and neuronal accumulation of sphingomyelin. Human beings exhibit five subtypes (A, B, C, D, and E) that differ in age of onset, lesion distribution, and sphingomyelinase activity. Feline models of Neimann-Pick disease of subtypes A and C have been recognized.[13,14] Clinical signs predominate as cerebrocortical and cerebellar dysfunction. Cuddon, Higgins, Duncan, et al described three cats with chemical changes consistent with type A Nieman-Pick disease that have predominant clinical signs of peripheral nerve dysfunction.[15] Tetraparesis, hypotonia, and areflexia develop between 2 and 5 months of age. Spontaneous activity is detected with needle electromyography (EMG), and motor and sensory conduction velocities are markedly slow. Light microscopy of peripheral nerves show severe demyelination and remyelination with vacuolated macrophages surrounding affected nerve fibers. Vacuolation and granular distentions are seen in neurons, glial cells, endothelium, choroid plexus, and ependymal cells. Macrophages with accumulations of granular material were dispersed throughout the central nervous system and body organs. Diagnosis is based on clinical signs and histopathology and biochemical evidence of reduced sphingomyelinase enzyme activity including tissue accumulations of sphingomyelin, cholesterol, and glycosphingolipids.

Globoid Cell Leukodystrophy

Globoid cell leukodystrophy (Krabbe disease) is an autosomal-recessive neurological disease that results from a deficiency in galactocerebrosidase (GALC) enzyme activity. The metabolic product of altered glycolipid metabolism, psychosine, is toxic to the myelin-forming oligodendroglial and Schwann cells. Globoid cell leukodystrophy has been well described in Cairn terriers and West Highland white terriers. Two separate reports exist of this disease in cats.[16,17] Because this leukodystrophy affects myelin in central and peripheral nervous tissues, clinical signs of CNS disease (tremors, blindness, dementia) tend to predominate. Pathology also exists in peripheral nerves. Histopathology reveals myelin loss with accumulation of lipid-filled macrophages (globoid cells) in the CNS and peripheral nervous system. No effective treatment exists, although several research groups are investigating gene expression in viral vectors.[18]

Glycogen Storage Disease Type IV in Norwegian Forest Cats

A deficiency in glycogen branching enzyme α-1,4-D-glucan: α-1,4-D-glucan 6-glucosyl transferase has been reported as an autosomal-recessive condition in Norwegian forest cats.[19-21] Clinical signs begin around 5 months of age with hyperthermia, generalized muscle atrophy, movement-associated whole body tremors, and ataxic gait. These progress rapidly to tetraparesis with diminished myotatic and flexor reflexes, multiple cranial nerve dysfunction, seizures, and eventually death. Serum biochemical abnormalities include transient elevations in alanine aminotransferase activity and creatine kinase activity reflective of hepatic dysfunction and muscle necrosis, respectively. Electrophysiological studies including electromyography, peripheral nerve conduction studies, electroen-

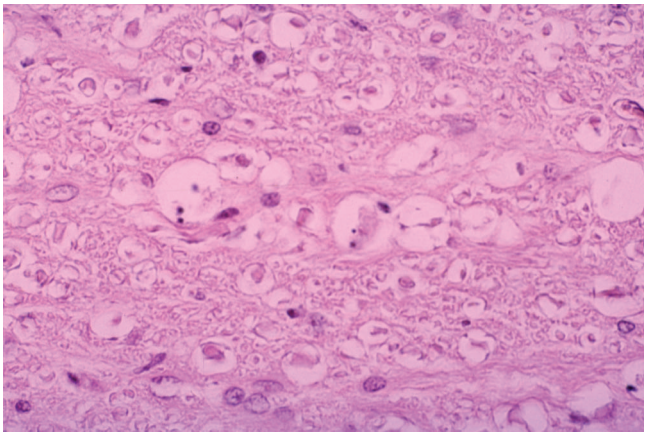

Figure 50-3. Histopathology of a nerve biopsy specimen from a Norwegian Forest cat with type IV glycogenosis. Note the presence of macrophage infiltration and evidence of axonal degeneration. (Courtesy Joan R. Coates and Kyle Braund, Auburn, AL.)

cephalography, and somatosensory evoked potentials reflect loss of both central and peripheral neurons. Histologically, accumulation of glycogen material detected by periodic acid Schiff-hematoxylin (PAS) stain occurs in multiple organs including lymph nodes, lungs, gastrointestinal tract, liver, thymus, cardiac and skeletal muscle, and central and peripheral nervous systems. Glycogen accumulations in neurons result in neuronal loss and axonal degeneration. Similar findings are observed in motor, sensory, and autonomic nerves (Figure 50-3). The genetic defect has been characterized, and a PCR screening test is available.[22]

Laminin α2–Deficient Muscular Dystrophy

Laminins are large glycoproteins that make up the basement membranes in a variety of tissues including muscle and Schwann cells. Although named muscular dystrophy, this syndrome actually involves nerves and muscles. In peripheral nerves, deficiency in laminin α2 affects the Schwann cells' ability to form myelin and results in a hypomyelinating neuropathy.

This disorder has been described in two cats, a DSH cat and a Siamese cat.[23] Both were female cats that were presented around 12 months of age for progressive weakness. Extensor contracture was a prominent feature in the DSH cat, whereas the Siamese was hypotonic and hyporeflexive in all four limbs. Both cats had marked increases in serum creatine kinase values, and motor nerve conduction velocities were reduced in the one case evaluated (the DSH). Dystrophic changes were present in all muscles evaluated, and demyelination of peroneal and radial nerves was noted. Immunocytological evaluation of muscle fibers showed decreased or absent laminin α2. Both cats were euthanized within months of diagnosis.

METABOLIC NEUROPATHIES

Diabetic Neuropathy

Peripheral neuropathy is a well-recognized consequence of diabetes in human beings and cats. The severity of neurological deficits in diabetic cats is highly variable, but common clinical signs include plantigrade stance, decreased spinal reflexes, muscle atrophy, a base-narrow gait, and irritability when manipulating the feet. Forelimb deficits are less noticeable.[24-26] In one study, electromyographic evaluation revealed scattered moderate spontaneous activity, whereas motor and sensory nerve conduction studies were significantly slowed. Evaluation of proximal nerve roots using F waves and cord dorsum latency measurements indicated that abnormalities extend the entire length of the nerves. Skeletal muscle biopsies reveal minimal neurogenic atrophy in muscles. Nerve biopsies show splitting and ballooning of the myelin sheath together with accumulations of Pi granules of Reich, lipid droplets, and intermediate filaments in Schwann cell cytoplasm. Myelinated fibers with inappropriately thin myelin sheath are present in addition to redundant Schwann cell membranes (onion bulbs) indicating demyelination and remyelination. Despite the myelin defects, most axons appear normal or shrunken.

The pathogenesis of diabetic neuropathy is not understood completely. A recent review highlights the most common theories.[27] Current areas of investigation include altered polyol pathway metabolism, inactivation of Na^+-K^+-ATPase activity, nonenzymatic glycosylation of structural proteins, and increased oxidative stress as a result of vascular damage. Regardless of the pathogenesis, clinical signs resolve with better glycemic control.

Neuropathies Associated with Thyroid Dysfunction

Hypothyroidism has been associated with peripheral nerve dysfunction in dogs.[28,29] No reports exist of this in cats, most likely because this diagnosis is infrequent in this species. On the other hand, hyperthyroidism is common in cats. Actual peripheral nerve dysfunction has not been evaluated carefully in these animals. In human beings, 20 per cent of hyperthyroid patients have signs of a sensorimotor axonal neuropathy early in the course of thyroid disease.[30] A significant percentage of hyperthyroid cats present with decreased ability to jump, reluctance to walk, and cervical ventroflexion.[31,32] Whether this represents actual peripheral nerve injury, muscle disease, or simply metabolic weakness is unclear.

NUTRITIONAL NEUROPATHIES

In general, peripheral nerve diseases in cats that can be attributed to dietary deficiencies or excesses are rare. Excess ingestion of pyridoxine (vitamin B_6) causes a severe sensory neuropathy in human beings, rats, and dogs.[33,34] Although no reports exist in cats, this species likely would not be immune to this disorder. Similarly, cats fed a diet deficient in aromatic amino acids (phenylalanine and tyrosine) also develop a pure sensory neuropathy.[35]

NEOPLASTIC NEUROPATHIES

Primary peripheral nerve tumors are uncommon in cats. Single case reports exist of a paraganglioma involving the cauda equina of a cat and an intestinal ganglioma in a young kitten.[36,37] Although still not common, several reports exist of malignant peripheral nerve sheath tumors (MPNST) in cats.[38-40] However, unlike dogs, MPNST often occur in peripheral nerves of the distal extremities (carpus, tarsus) or superficial nerves of the trunk or head in cats. Clinical signs of tumors in these regions generally consist of irritation or pain. Radiographically, lytic or

sclerotic changes in underlying bone are common. Surgical excision may be curative. However, incomplete resection of neoplastic cells results in regrowth of the tumor.

Infiltration of cranial and spinal nerves by neoplastic lymphocytes also results in clinical signs of peripheral nerve dysfunction in cats.[41-44] Many of these cats are feline leukemia virus (FeLV) positive and have multicentric disease. When involving spinal nerves, extension into the spinal canal can cause cord compression. Occasionally, neoplastic lymphocytes are present in cerebrospinal fluid, but the diagnosis usually is confirmed with fine-needle aspiration or biopsy of involved tissues. Chemotherapy or irradiation may be beneficial. Unfortunately, long-term prognosis in most cases is poor.

INFLAMMATORY INFECTIOUS NEUROPATHIES

Sporadic reports of peripheral nerve disease in cats infected with either FeLV or feline immunodeficiency virus (FIV) have appeared in the literature. Anisocoria, mydriasis, and abnormal pupillary light reflexes are seen commonly in FeLV-positive cats.[45] This is thought to be caused by injury to the short ciliary nerves in the retrobulbar space.[46] Other neuropathies associated with FeLV infection have not been well documented. Evidence for FIV-associated peripheral neuropathy is more compelling. In two separate reports, generalized peripheral nerve disease was caused by infection with experimental strains of FIV.[47,48] Infected cats had clinical evidence of motor weakness and decreased peripheral nerve conduction velocities. Histologically, axonal injury involving both large- and small-diameter fibers was observed in one study 12 weeks after infection.[48] Infiltrates of macrophages were seen in the perineurium and endoneurium in addition to dorsal root ganglia. These lesions were associated with high viral RNA levels in peripheral nerves.

IDIOPATHIC NEUROPATHIES

Brachial Plexus Neuritis

A single case of focal inflammatory neuritis involving only the brachial plexus of a cat has been reported.[49] A 4-year-old male, neutered cat developed an acute onset of forelimb weakness with normal rear limb function over a 24-hour time period. Nerve conduction velocities in the median nerve were severely slowed, which indicates demyelination. The cat improved within 3 weeks with minimal therapy. Vaccination 27 days before the onset of clinical signs was thought to have initiated an immune reaction.

Idiopathic Polyradiculoneuritis

An acute, generalized polyradiculoneuritis similar to coonhound paralysis in dogs occurs infrequently in cats.[50-52] Of the reported cases, age of onset varied from 3 months to 4 years of age. Affected cats develop ascending, flaccid tetraparesis within 72 hours from the onset of clinical signs. In one study, respiratory compromise resulted in euthanasia in two of nine cases, whereas the remaining seven patients improved without medication within 4 to 6 weeks.[51] Fever, icterus, and anemia were associated signs in one case.[52] Histologically, axonal loss, demyelination, and accumulation of macrophages were found in ventral nerve roots of two cats and along multiple sites of peripheral nerves in one cat. An immune-mediated cause has been proposed for dogs and cats. Diagnosis is based on history, clinical signs, and abnormal electrophysiology. Electrodiagnostic findings include diffuse electromyographic abnormalities, slowed nerve conduction velocities, and absence of small evoked motor potentials referred to as F waves. Treatment consists of supportive care. Despite the probable immune-mediated pathogenesis, immunosuppressive therapy in other species suggests the probability of secondary infections and muscle atrophy.

Chronic Inflammatory Demyelinating Polyneuropathy

In numerous clinical descriptions, cats with peripheral nerve disease follow a remitting and relapsing course.[53-57] The onset may be acute or more insidious. Some cats also have megaesophagus and regurgitation. Electromyography can be normal or shows patchy areas of spontaneous activity. Motor nerve conduction velocities are slowed, which suggests a primary demyelinating condition with limited axonal degeneration. Histologically, peripheral nerves have patchy demyelination and remyelination with occasional axonal degeneration. Ultrastructurally, inflammatory cells including macrophages, lymphocytes, and mononuclear cells are found within the endoneurium. The amount of inflammation varies between nerves and may reflect the stage of the disease process. The majority of patients respond to immunosuppressive doses of corticosteroid (prednisolone 1 to 2 mg/kg PO daily) gradually tapered to the lowest effective dose or discontinued in some cases. Relapse of clinical signs can occur after discontinuation of corticosteroids. Occasionally, steroid resistance can develop, which causes deterioration of clinical signs during treatment. The pathogenesis for this class of neuropathies remains an enigma. Based on histological appearance of an inflammatory response against peripheral nerve myelin and the response to immunosuppressive therapy, an immune-mediated cause is suspected.

Motor Neuron Disease

A slowly progressive weakness attributable to loss of motor neurons similar to amyotrophic lateral sclerosis was reported first in adult cats.[58] In all cases, the weakness progressed for months to years before the animals were euthanized. Clinically, these cats were indistinguishable from those with axonopathies. Ventral horn involvement was confirmed at necropsy. More recently, a colony of cats has been established with identical clinical signs and histological appearance.[59] The inheritance pattern is presumed autosomal recessive.

TRAUMATIC NEUROPATHIES

Peripheral nerve injury can occur subsequent to traumatic processes. Most present as a monoparesis. Clinical signs associated with injury to specific peripheral nerves have been described.[60] The most common cause of traumatic neuropathy that involves larger groups of nerves is avulsion of the brachial plexus. Because nerve roots lack a perineurium, traction of the forelimb or severe abduction of the scapula frequently results in avulsion of these nerve roots, usually within the dura near the intervertebral foramen.[61] In addition to monoparesis, loss of

sympathetic innervation to the face (Horner's syndrome) and dysfunction of the lateral thoracic nerve (efferent for cutaneous trunci reflex) are common because of proximity of these nerves to the brachial plexus. As with all traumatic nerve injuries, waiting for 4 to 8 weeks before rendering a prognosis is important, because almost all injuries are associated with loss of nerve function without loss of axonal integrity (neuropraxia). If loss of axonal integrity (axonotmesis) or complete transection of the entire nerve (neurotmesis) occurs, the prognosis for functional return is guarded. Peripheral axons regrow but do so only at a rate of 1 to 2 mm per day. If the entire nerve has been transected, regrowth is unlikely, even if surgical repair is attempted. This usually is attributed to malorientation of endoneural structures and disruption of paths for regenerating axons to migrate through. Although brachial plexus avulsions historically have carried an extremely poor prognosis, experimental attempts to reimplant avulsed nerve roots in cats have shown encouraging results.[62-64]

TOXIC NEUROPATHIES

Peripheral neuropathy can occur with exposure to a number of toxic substances. Despite this, toxin-induced neuropathies are diagnosed rarely in clinical practice. Inability to identify toxin exposure in free-roaming pets, together with a relative lack of accessible screening tests for blood or tissues, may contribute to the infrequency of this diagnosis. Certainly toxic neuropathies should be considered in cats with neuropathy resulting from an unknown cause. The well-documented toxic neuropathies in cats are discussed.

Chemical

Cats are more susceptible to neuropathic effects of several chemicals, notably organophosphates and acrylamide, than many other species.[65-70] Cats have been used as a common model to study the central-peripheral distal "dying back" neuropathies induced by these chemicals. During the acute phase of intoxication, generalized tremors and profuse salivation are seen as consequences of cholinesterase inhibition. However, after 1 to 4 weeks, signs of generalized weakness and areflexia develop. Histologically, organophosphate toxicity is characterized by distal, nonterminal degeneration of axons in both the central and peripheral nervous systems. Acrylamide causes characteristic axonal swellings that contain unorganized filamentous structures. Despite decades of intensive study, the exact pathogenesis of both of these neuropathies is not known.

Heavy Metal

Cats are especially susceptible to heavy metal intoxication. Thallium toxicosis, found in some rodenticides, causes a sensory neuropathy, whereas methylmercury causes degeneration of both sensory nerves and central neurons.[71-73] In the latter case, seizures overshadow clinical signs of peripheral involvement.

Drugs

Experimentally, vinca alkaloids (i.e., vincristine) cause a proximal axonal neuropathy resulting from disruption of neurofilaments in cats.[74] Another drug recognized to cause peripheral nerve disease in cats is salinomycin. A series of cats in Switzerland and the Netherlands developed distal axonal degeneration when exposed to salinomycin (a coccidiostat) contamination of cat food.[75] Both drugs produce similar clinical signs of weakness and diminished spinal reflexes that resolve when the drug is discontinued.

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Chapter 51

Miscellaneous Spinal Cord Diseases

Robert L. Bergman

Spinal cord diseases in cats vary in the severity and in progression of neurological dysfunction. Diagnosis of spinal cord disease in cats can be a challenge. Clinical signs often are vague and insidious. Advanced imaging techniques have improved diagnostic capabilities and recognition of new disorders. Infectious inflammatory disease is the most common categorical differential diagnosis in cats with spinal cord dysfunction. Other common disease categories include neoplasms, trauma, and degenerative disorders.[1] Veterinarians must think beyond the more common differential diagnoses to consider unusual diseases and different diagnostic approaches. This chapter emphasizes newly recognized spinal cord diseases and provides a review of the current literature.

DIAGNOSTIC EVALUATION

Signs of neurological dysfunction dictate the neuroanatomical localization of a lesion within the spinal cord. Spinal reflexes and paraspinal hyperesthesia assist with lesion localization. Localization is specified to the spinal cord regions C1-C5, C6-T2, T3-L3, and L4-S2, based on upper motor neuron or lower motor neuron signs of limb weakness. Cats with spinal cord compressive disease or meningomyelitis often exhibit paraspinal hyperesthesia. Pathology of the spinal cord tissue itself usually does not have hyperesthesia as a clinical sign. Orthopedic, polyneuropathic, myopathic, and neuromuscular junction disorders can mimic signs of spinal cord dysfunction. Careful interpretation of the neurological examination differentiates among these disorders (see Chapter 49).

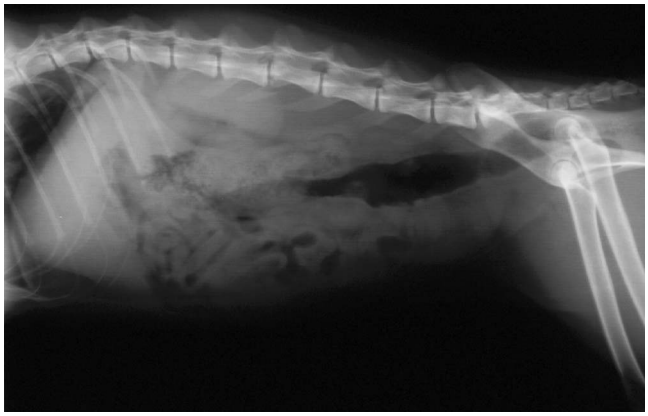
Signalment and history aid in formulation of a list of probable differential diagnoses. Young cats are more likely to be diagnosed with feline infectious peritonitis (FIP), lymphosarcoma, or a congenital anomaly. Middle-age and older cats may be diagnosed with nonlymphoid neoplasia or intervertebral disc disease. History is important for determining temporal onset (acute, insidious, or episodic) and progression (rapid, gradual, or static). Trauma, vascular insults, and some inflammatory and neoplastic diseases present acute in onset.

Cats with spinal cord dysfunction require thorough physical examination and routine laboratory diagnostic testing. Other disorders that cause paresis can mimic spinal cord disease; for example, neuropathy, myopathy, junctionopathy, polyarthropathy, and cardiovascular disease. Routine laboratory testing consists of a complete blood count (CBC), serum chemistry profile to include creatine phosphokinase (CK) enzyme activity, and urinalysis. Evaluation of CK activity aids in identification of a myopathy, which can mimic spinal cord dysfunction. Patient infection with feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV) must be identified. Additional serology for infectious disease is dependent on suspicion of other diseases.

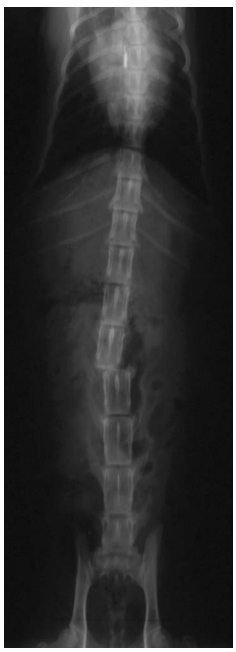
Survey radiography of the spine is recommended for cats with spinal cord dysfunction. Sedation or general anesthesia often is necessary to allow for proper patient positioning and relaxation of the spine. Some findings are nonspecific, but discospondylitis, vertebral tumors, or spinal trauma usually have more obvious radiographic abnormalities. Orthogonal or multiple views are recommended strongly, because a single view may not always provide complete information about the extent of the lesion (Figure 51-1).

Myelography consists of injection of a nonionic contrast medium (0.3 to 0.45 ml/kg of iohexol [240 mg/ml] or iopamidol [200 mg/ml]) into the subarachnoid space of the low lumbar spine (L6-L7 or L5-L6) or the cerebellomedullary cistern. Myelography is an imaging technique used commonly to identify the location and extent of spinal cord compression.[2] Additional information may be used when combining the myelographic findings with computed tomography (CT). Magnetic resonance imaging also is a more sensitive technique for evaluation of the spinal cord tissue.

Cerebrospinal fluid (CSF) analysis is useful for detection of evidence of spinal cord disease, particularly when an inflammatory disorder is suspected. However, in most cases, a definitive diagnosis is not provided by CSF analysis alone, even in cats with overt CNS inflammatory disease.[3] Exceptions include finding the inciting organism in the CSF (e.g., *Cryptococcus neoformans*) or identifying neoplastic cells (e.g., lymphosarcoma).[3] Collection of fluid from the lumbar region may be preferable, because CSF flows in a caudal direction.[4] Additional diagnostic procedures include electrophysiology, CSF protein electrophoresis, serology, and exploratory surgery.



A



B

Figure 51-1. A, A lateral survey spinal radiograph of a mild subluxation of L4. **B,** A ventrodorsal spinal radiograph with more severe evidence of luxation in the same cat. This cat did not have deep pain perception.

SPINAL CORD DISEASES

Infectious Inflammatory Diseases

Infectious inflammatory diseases account for 31 per cent of all feline spinal cord diseases.[1] Common infectious inflammatory spinal cord diseases include FIP, cryptococcosis, FeLV infection, and toxoplasmosis.

Bacterial Diseases

Approximately 15 per cent of cases of meningomyelitis in cats are bacterial or suspected to be bacterial in origin.[1] Bacterial infections may occur secondary to hematogenous spread or, more likely, as a result of direct extension of a local wound (e.g., cat bite abscess).[5] *Pasteurella* spp. and *Staphylococcus* spp. are common pathogens. Discospondylitis often is caused by a bacterial infection and involves the intervertebral disc and associated vertebral endplates. Discospondylitis has been reported infrequently in cats and, if not treated appropriately, may progress to severe neurological dysfunction.[6,7] Polioencephalomyelitis, an inflammatory disease of unknown cause, is associated with 8 per cent of cases of feline spinal cord disease[1] and may present with clinical signs of paraparesis.[5] Although not well described in the literature, eosinophilic/histiocytic meningomyelitis accounted for 6 per cent of inflammatory spinal cord diseases in cats.[1]

Viral Diseases

FELINE IMMUNODEFICIENCY VIRUS. FIV has been reported to cause a degenerative myelopathy that can be detected histologically with changes including myelin sheath splitting and intramyelinic vacuoles. Clinical signs of spinal cord dysfunction are not evident in experimentally infected cats or in cats with naturally occurring FIV infection.[8]

FELINE INFECTIOUS PERITONITIS

Presenting Signs and Pathogenesis. FIP accounts for more than half of the infectious inflammatory causes of myelitis in cats, and 16 per cent of all spinal cord diseases reported in cats.[1] Clinical signs of FIP result from the immune response of susceptible cats when infected by a mutant form of the feline enteric coronavirus (FECV), which reproduces within macrophages.[9,10] The dry, or noneffusive, form of the disease is associated most commonly with CNS signs as opposed to the "wet" or effusive form, which involves the visceral organs and causes abdominal effusion. Pyogranulomatous inflammatory lesions involve the meninges, choroid plexus, and ventricular system. The immune response associated with FIP causes a vasculitis and an ependymitis that subsequently may obstruct flow of CSF.[11] Signs of systemic illness occur in approximately 79 per cent of cats with FIP.[1] Typical signs include weight loss, anorexia, intermittent fever, and ocular changes (anterior uveitis or chorioretinitis).

About one third of cats with FIP have presenting clinical signs of neurological dysfunction.[12] Young, purebred, sexually intact male cats are at a higher risk for developing FIP.[13] A genetic susceptibility of about 50 per cent exists for development of FIP.[10] All cats in one study of patients with neurological signs of FIP were from multiple-cat households.[9] Although younger cats are most susceptible to FIP infection, cats of any age can develop the disease. In a case series of cats with spinal cord–related signs, more than 75 per cent were younger than 2 years of age.[1]

Most cats with FIP have intracranial signs but often manifest signs of spinal cord dysfunction: pelvic limb ataxia, generalized ataxia, and paraspinal hyperesthesia. In a small case series of cats with confirmed FIP, four of 10 had paresis or paralysis as the presenting clinical sign.[12] Paresis was evident in two of seven of these cats with diffuse FIP.[12] In another study, 28 of 29 cats with FIP had histological lesions that predominated in the cervical spinal cord and brain.[1]

Diagnosis. Antemortem diagnosis of FIP is difficult. Diagnosis is suspected based on assimilation of history, signalment, hematology, and other supportive diagnostic tests that include serology, CSF analysis, findings on imaging, and tissue biopsies. A typical history includes acquisition of the cat from a cattery or shelter, and a fever that waxes and wanes and does not improve with antibiotic therapy.[10] Common hematological and biochemistry abnormalities include neutrophilia or lym-

phopenia, low albumin with increased globulins, or a high serum fibrinogen.[10]

Serological testing and polymerase chain reaction studies to assess for viral load can be beneficial.[10] Serology only confirms exposure to feline coronavirus. Some cats with FIP may have high antibody titers, but this is not absolute. A recent study of histopathologically confirmed cases of FIP found that serological testing provided further support for tissue biopsy procedures.[14] High antibody titers (1:1600) provide a 94 per cent probability of active FIP infection.[14] A titer that was positive but below 1:1600 suggested only a 44 per cent probability that cats had FIP.[14] The titers in 10 per cent of cats with FIP were negative, which suggests a compromised immune system.[14] Definitive diagnosis of FIP is made by histopathology of abdominal organs obtained by tissue biopsy. Immunofluorescent assay/immunohistochemistry techniques can detect presence of coronavirus antigens within macrophages.[14]

Diagnostic evaluation of the CNS aids in an indirect diagnosis of FIP. Results of CSF analysis often reveal a marked increase in protein concentration and a neutrophilic pleocytosis.[11,15] Comparisons of antibodies in serum and CSF may provide additional information, but false negatives and false positives are possible. Presence of antibodies in CSF must be interpreted in light of blood-brain barrier breakdown. Adjunctive comparison of other infectious disease antibody titers in serum and CSF can assist with determination of intrathecal production of antibodies.[10] Common abnormalities on MRI and CT include presence of hydrocephalus and periventricular contrast enhancement. Overall the most consistent diagnostic findings in cats with the CNS form of FIP include a positive coronavirus IgG titer in CSF, a high serum total protein concentration, and abnormalities in brain imaging.[9]

Treatment. No treatment has been proven effective for FIP, and the long-term prognosis is poor.[10] Overall mortality rate is 95 per cent.[10] Supportive therapies consist of antiinflammatory doses of prednisone (1 mg/kg/day PO) and immunomodulation with cyclophosphamide or interferon. A recent report found use of recombinant feline interferon combined with corticosteroids more effective in cats with the effusive form than with the noneffusive form (n = 1) of FIP.[16] Other therapeutic recommendations include a diet with high nutritional value and stress reduction.[10]

Cryptococcosis

Presenting Signs and Pathogenesis. *Cryptococcus neoformans* is a saprophytic fungal organism that can cause systemic or focal disease. Transmission occurs through inhalation of the organism that lives in the soil or bird excrements. CNS signs are reflective of meningitis or focal granuloma formation within the brain parenchyma. Fungal masses within the extradural space cause secondary compression (Figure 51-2).[17] Cryptococcal infection can cause focal spinal cord disease in some cats. The mean age for cats infected with *Cryptococcus* is 6 years; however, the age range can vary.[18,19] Approximately 58 per cent of cats diagnosed with *Cryptococcus* spp. were considered primarily outdoor cats.[18]

Systemic signs are variable and commonly include depression/lethargy, fever, poor body condition, or anorexia.[18] In one case series, approximately 50 per cent of the cats with cryptococcosis had CNS signs, 42 per cent had ocular signs, and 32 per cent had respiratory signs.[18] Cutaneous lesions also can occur. Another case series reported that only 9 per cent of cats showed signs of neurological dysfunction. In this series, nasal signs were more common.[19] Clinical signs of spinal cord dysfunction, including paraspinal hyperesthesia and paresis, have been reported in at least one case series.[18] *C. neoformans* accounted for 9 per cent of infectious causes of spinal cord disease in cats.[1]

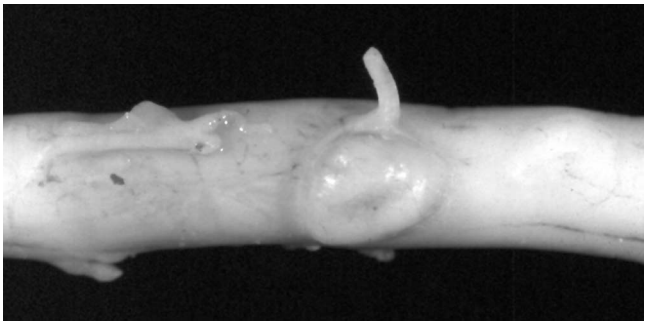


Figure 51-2. *Cryptococcus neoformans* infection can cause focal spinal cord disease in cats. This picture depicts a fungal granuloma present on the spinal cord.

Diagnosis. CSF analysis is one of the most useful diagnostic tests in cats with CNS cryptococcosis. Neutrophilic and eosinophilic pleocytosis often are present. In some cases, the organism is identified. Diagnosis also is based on detection of capsular antigen using a latex agglutination test in serum and CSF. Cats with focal granulomas in the CNS may have negative antigen titers.[17] Latex agglutination tests can have false-negative results (or interference), which makes definitive diagnosis difficult.[18] In these cases, cultures, cytology, or histopathology of other tissues, such as skin, may be necessary. Also important is documentation of the FeLV and FIV status of cats with cryptococcosis, because concurrent infection may be common.[18] Additionally, cats with other concurrent viral infections tend to have a higher incidence of treatment failure.[20]

Treatment. Treatment of CNS cryptococcosis consists of long-term administration of systemic antifungal agents. Itraconazole and fluconazole are considered the drugs of choice. Fluconazole (5 to 15 mg/kg PO q12h) is recommended, because it crosses the blood-brain barrier readily and has high lipid solubility. Duration of treatment ranges from 6 to 10 months; however, a longer duration may be required to prevent relapse.[21,22] Antiinflammatory doses of corticosteroids help to decrease the inflammation and edema that can worsen neurological signs during treatment. Therapeutic monitoring is based on clinical response and serial serum antigen titers. Antigen titers often remain positive for a considerable period of time after clinical signs have resolved.[19] Cats that have a reduction in antigen titer during the course of treatment have a better prognosis.[20] Surgical removal of a fungal granuloma may be considered in conjunction with antifungal therapy.[17]

Toxoplasmosis

Presenting Signs and Pathogenesis. *Toxoplasma gondii* is an infrequent cause of spinal cord disease in cats; it was reported as the cause for only 3 per cent of all infectious diseases resulting in spinal cord dysfunction.[1] *T. gondii* is a protozoal coccidian parasite for which cats are the definitive host. Transmission occurs congenitally through the placenta from an infected queen or more commonly by ingesting the organism.

Healthy cats may be positive on serology but rarely develop clinical disease. Predisposing factors for clinical disease include immunosuppression as a result of FIV and/or FeLV infection, administration of corticosteroids or chemotherapy, and diabetes mellitus. Toxoplasmosis causes a nonsuppurative meningoencephalomyelitis. The organism also may infect muscle and peripheral nerves.[5] Systemic signs include anorexia, weight loss, fever, and pneumonia.

Diagnosis. Definitive diagnosis of toxoplasmosis is difficult. A suspected diagnosis is based on clinical signs, the exclusion of other CNS diseases, serology, and response to treatment.[11] The amount of CSF pleocytosis is variable, and the cellular differential count usually consists of mononuclear cells. Albuminocytologic dissociation may be the only abnormality. *T. gondii*–specific IgG and IgM can be assayed in serum and CSF. Paired titer evaluations may detect an increase in serum IgG; however, the disease course still may be static.[11] An IgM titer greater than 1:256 may indicate an active or recent infection. Antibodies in CSF are compared with serum antibody titers for accurate interpretation of blood contamination and intrathecal antibody production. A definitive diagnosis is made by detecting the organism in a tissue biopsy.

Clindamycin (12.5 mg/kg PO q12h for 4 weeks) is recommended for treatment of CNS toxoplasmosis.[23] An alternative drug therapy is trimethoprim-sulfonamide (15 mg/kg PO q12h).[23] One author reported a fair to good outcome in three cats treated for *Toxoplasma*-induced myelitis.[5] Clinical signs can be residual and response to therapy may be slow.[11]

FeLV Myelopathy

Clinical Presentation and Pathogenesis. Feline leukemia virus, an oncogenic retrovirus, can cause spinal cord dysfunction. FeLV can cause myelopathy by indirect and direct pathogenic mechanisms. FeLV can predispose to the spinal form of lymphoma indirectly or cause a degenerative myelopathy directly. FeLV-associated myelopathy reflects primary pathology within the spinal cord.[24] Light microscopic examination revealed swollen axons and myelin sheaths in the brain stem and spinal cord of affected cats. Immunohistochemical staining revealed FeLV antigens in neural tissue. A previously reported case of degenerative myelopathy in a FeLV-positive cat may have been FeLV-associated myelopathy.[25]

This disease is associated with chronic infection with FeLV. CNS signs develop on average 3 years after the first positive FeLV test.[24] Mean age of affected cats is 9 years.[24] Signs of FeLV-associated myelopathy include progressive ataxia and hyperesthesia, and paralysis develops within 1 year after onset of paraparesis.[24] Urinary incontinence occurs in a small percentage of cats.

Diagnosis and Treatment. A suspected antemortem diagnosis is based on ruling out other diseases. Positive FeLV tests should heighten suspicion for this disease. CSF analysis usually is not helpful.[24] Advance imaging studies have not been evaluated in cats with FeLV-associated myelopathy. Myelography is normal. No treatment options have been described.

Neoplastic Disease

Neoplasia is a common cause of spinal cord dysfunction in cats. With regard to relative incidence in one case series, neoplasia affected 28 per cent of cats diagnosed with spinal cord dysfunction.[1] Lymphosarcoma made up 38 per cent of neoplasia-related spinal cord cases; however, this disease is becoming less common with the reduction in incidence of FeLV infection.[1,26,27]

Lymphosarcoma

Presenting Clinical Signs and Pathogenesis. Spinal lymphoma historically has been the most common cause of spinal cord neoplasms in cats. CNS lymphoma accounted for 12.1 per cent of all cases of lymphoma and, of these cases, 88 per cent had spinal cord involvement.[28] The disease is especially common in young FeLV-infected cats, with a mean age reported between 3.6 and 4 years.[28,29] Cats younger than 3 years of age make up approximately 70 per cent of the cases.

Clinical signs associated with spinal lymphoma may be associated with a focal myelopathy that can occur in any region of the spinal cord. Paresis has been reported in approximately 80 per cent of cats with spinal lymphoma.[28,29] Evidence of spinal hyperesthesia may be focal or multifocal with more extensive distribution.[29]

The disease course can be rapidly progressive, with some cats showing signs for a week or less.[28,29] Neurological signs are related to the location of the lymphoma. Although lymphosarcoma generally is a multicentric disease, more than 85 per cent of cats with CNS involvement lack systemic signs or hematological changes.[29] Renal lymphoma is likely to metastasize to the CNS.

Diagnosis. Evidence for systemic disease on physical examination includes enlargement of lymph nodes and abdominal organs. A CBC may show anemia, leukopenia, and thrombocytopenia. Circulating lymphoblasts may be present on a differential white blood cell count. A positive correlation between serological testing and spinal lymphoma has been reported.[28,29] The safest and most reliable method of obtaining a diagnosis of CNS lymphoma is confirmation of the presence of lymphoma in other visceral organs. Bone marrow aspiration may be diagnostic for neoplasia in up to 81 per cent of cases with this disease.[29] CSF analysis is not always diagnostic for lymphosarcoma because of its extradural location. One case series reported that 6 of 17 cats had neoplastic lymphocytes in the CSF.[28] Myelography can determine lesion extent and detect presence of extradural, intradural-extramedullary, or intramedullary involvement. An extradural lesion is the most common myelographic finding. Fluoroscopic aspiration and cytology may allow definitive diagnosis of the spinal lesion.[29] MRI may detect intramedullary lesions.

Treatment. Positive FeLV status in cats has been shown to be a negative prognostic indicator for spinal lymphoma.[30] The prognosis for cats with paresis or paraplegia is considered poor. Treatment options for spinal lymphoma consist of chemotherapy, surgical resection, and focal irradiation.[31] No superior treatment strategy for chemotherapy has been documented. Currently, multidrug protocols are advocated.[27,29] A laminectomy procedure facilitates diagnosis and decompression until other therapies can take effect.

Nonlymphoid Neoplasia

Clinical Presentation and Pathogenesis. Nonlymphoid tumors involving the spinal cord are less common in cats. Tumors may be categorized based on expected locations: intramedullary, extramedullary/intradural, and extradural.

Intramedullary tumors are considered uncommon and make up 10 per cent of all reported spinal cord neoplasms in cats.[1] Documented tumors include astrocytoma and ependymoma.[32,33] Intradural/extramedullary tumors make up 12 per cent of spinal neoplasia cases and include meningiomas, meningeal sarcomas, and malignant nerve sheath tumors.[1] Feline meningiomas usually occur rostral to the foramen magnum; only 4 per cent of meningiomas found in cats affected the spinal cord.[34] Levy, Mauldin, Kapatkin, et al reported five cases of spinal meningiomas in cats: one in the cervical region, three in the thoracic spine, and one in the lumbar spine.[36] Another case report described a meningioma affecting the spinal cord at the C6-C7 spinal cord segment.[35]

Extradural spinal cord compression can result from spinal canal masses or tumors of the surrounding bone and vertebrae. These make up about 40 per cent of spinal cord–associated neoplasms in cats, with vertebral and bone tumors accounting specifically for 29 per cent of all spinal tumors.[1] Reported tumor types include chondrosarcoma, lipoma, osteosarcoma, and multiple myeloma.[36] Nonlymphoid spinal neoplasia typically occurs in older cats, with a median age of 12 years in one case series.[36] These tumors are not associated with FeLV or FIV infection.

Clinical signs of myelopathy are dependent on tumor location. Focal pain and paresis are most typical. Intramedullary neoplasms usually do not cause spinal hyperesthesia until later in the disease course. The clinical course of spinal neoplasms also varies. Chronic progressive spinal dysfunction may be expected; however, peracute signs (e.g., pathological vertebral fracture) may present (Figure 51-3).

Diagnosis. The process of diagnosis of nonlymphoid tumors begins with survey spinal radiographs. Evidence of bony lesions can be evident in osteosarcoma and multiple myeloma. Myelography determines extent and location of spinal involvement. Advanced imaging (CT and MRI) may assist further with determination of lesion extent. Findings on CSF analysis often are nonspecific. Fluoroscopic aspiration or surgical biopsy may yield a definitive diagnosis.

Treatment. Specific treatment regimens are based on histopathological diagnosis of the tumor. Treatment often consists of palliative corticosteroids (i.e., prednisone 0.5 to 1 mg/kg/day PO) to control edema, and pain management. Surgical removal/debulking of various tumor types has been described and may improve survival times.[36] A reasonable survival time can be expected for cats with meningiomas after surgical resection.[36] Osteosarcomas may be associated with long survival times and appear to be less aggressive than the canine form of this disease.[36] A treatment regimen reported for multiple myeloma in a Maine coon cat 6 years of age consisted of a combination of chemotherapy and irradiation.[37]

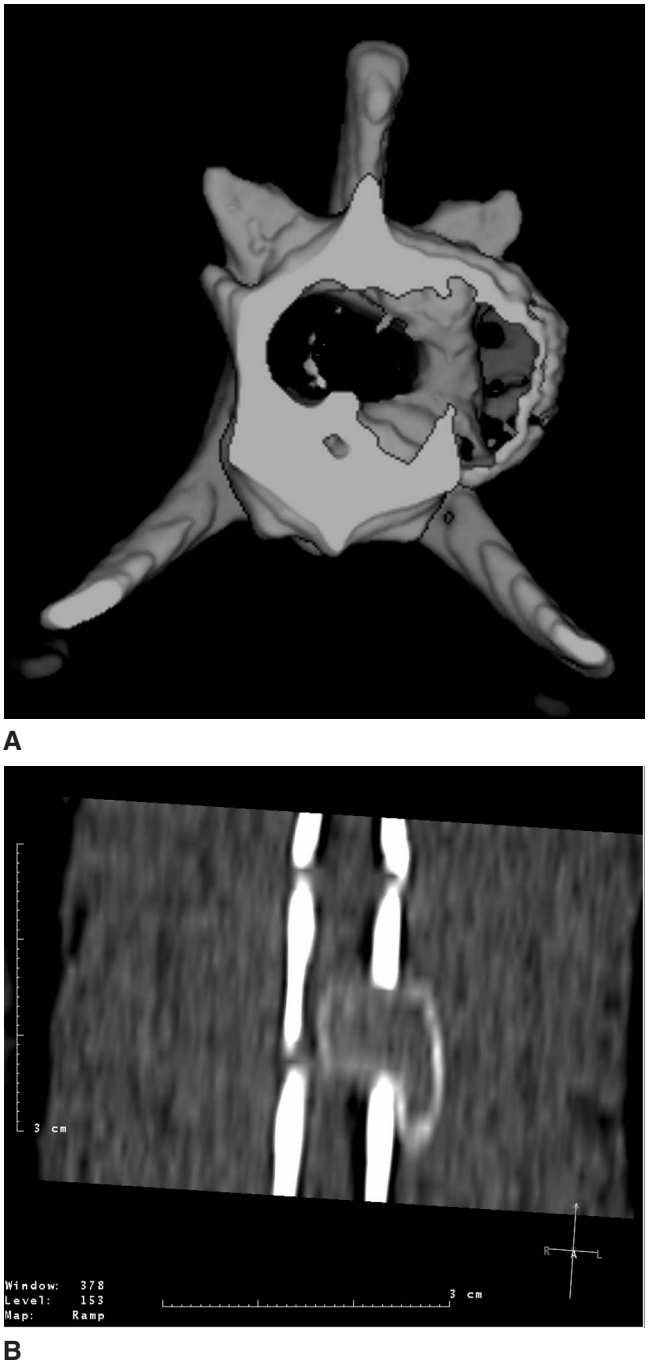


Figure 51-3. Reconstructed CT images of an osteosarcoma involving the vertebral body of L2 from a 9-year-old spayed female domestic shorthair cat. **A,** Three-dimensional reconstruction. **B,** Dorsal planar view of a two-dimensional reconstruction. The mass was removed surgically and the cat lived for an additional 2 years before the mass recurred. (Images courtesy Jeryl Jones, Virginia-Maryland Regional College of Veterinary Medicine, Blacksburg, Virginia.)

Spinal Trauma

Clinical Presentation and Pathophysiology. Spinal trauma is an important cause of spinal cord dysfunction in cats. Cats have been the subject of multiple laboratory studies of spinal cord injury.[38-44] Information learned from this research must be interpreted from the standpoint that the mechanism of spinal cord trauma is controlled in the laboratory environment. Naturally occurring spinal trauma in cats is not a well-described phenomenon because cats often do not survive the inciting incident.

Spinal injury occurs more frequently in younger cats. Cats (n = 69) in a retrospective study of spinal injury were 9 years of age or younger; 39 per cent were younger than 1 year of age, and 29 per cent were between 1 and 3 years of age.[45] The mean age of another study of 30 cats was 3.6 years (range 2 months to 12 years).[46]

Common causes of spinal trauma are height-related and vehicular injuries. In a large report of high-rise syndrome in

cats, 10 per cent sustained spinal fractures or luxations.[47] Other sources of trauma include dog attacks and gunshot wounds.[45,46] Compression-type fractures occur in more than two thirds of the cases with spinal fractures.[46] Twenty per cent of cats with spinal injuries also have acute disc extrusions secondary to the trauma.[46] Spinal cord contusion injury without evidence of fractures also may occur after a fall.[46] Other injuries that occur in conjunction with spinal trauma include pneumothorax, pulmonary contusions, abdominal organ trauma, and head trauma.

Although all segments of the spine are susceptible to trauma, the cervical and sacral/caudal regions are much less likely to sustain injury. The thoracic and lumbar regions make up 51 per cent and 32 per cent of spinal column injuries, respectively.[45] Traditionally, the most likely location for spinal column injury is at a site characterized by a transition from rigid stability to less stability, such as T13-L1 or L7-S1. This was challenged recently in a larger study consisting of 69 cats, in which 51 per cent of the spinal trauma cases occurred between T8 and T12.[45] The segments between L2-L3 and L4-L5 also were significant sites in 43 per cent of the cases. The T11 through T12 vertebrae have been reported to be affected in 45 per cent of spinal injuries in cats.[46] A case series reported by Voss showed that 50 per cent of spinal fractures were located between the L3 and L6 vertebrae.[48]

Diagnosis. In cases of suspected spinal injury, the neurological examination is performed with caution to minimize movement of the cat with suspected spinal instability. Evaluation of deep pain perception is most important with regard to determining prognosis.

Spinal radiography using orthogonal views should localize the lesion. Radiography documents spinal alignment during that time without knowledge of the amount of displacement at the time of the injury. The entire spine should be radiographed, because multiple spinal fractures are common. Advanced imaging of the spine has been recommended because plain film radiography and myelography may underestimate the degree of fractures or luxations present.[48] Myelography or MRI defines the extent of spinal cord compression more accurately.[46]

Treatment. Goals of therapy are to prevent further mechanical damage to the spinal cord and reduce secondary injury processes. Treatment recommendations often are adapted from laboratory studies that involve species other than cats. Drawing firm conclusions for optimal treatment of spinal trauma in cats is difficult.

Management of a cat with spinal trauma should focus first on systemic stabilization. Management consists of following the ABCs of trauma. Airway is assessed for patency and adequate ventilation. Appropriate fluid therapy helps to maintain cardiovascular function. Aggressive fluid therapy is important to maintain spinal cord perfusion.[49] Hypotension is one factor shown to worsen outcome in human beings with spinal cord injury. Isotonic crystalloids (lactated Ringer's solution or 0.9 per cent sodium chloride) at shock doses, initially (60 ml/kg/hr IV in cats) are given to effect until heart rate, capillary refill time, and pulse quality improve. Hetastarch (6 per cent) is a large molecular weight colloid that consists of a branched polysaccharide, amylopectin. Its molecular properties provide a long intravascular half-life. The dose is 10 to 20 ml/kg given to effect up to 40 ml/kg/hr. Hetastarch is administered intravenously to cats to effect up to 10 to 15 ml/kg; the dose is increased in 5 ml/kg increments every 5 to 10 minutes to avoid nausea and vomiting. Hypertonic saline (7 per cent) also may be used to expand blood volume quickly. The dose (4 to 5 ml/kg) is administered as an intravenous bolus over 3 to 5 minutes. The disadvantage associated with the use of hypertonic saline is that it remains in the vascular space for only 15 to 60 minutes. Blood products also are used to expand volume and provide increased oxygen delivery. Whole blood is administered intravenously at a dose of 4 to 10 ml/kg/hr, over 4 to 6 hours in stable patients and faster in unstable patients. The goal is to restore the hematocrit to 25 to 30 per cent and albumin to more than 2 g/dL.

Use of high-dose methylprednisolone sodium succinate (MPSS) is becoming more controversial but is still considered standard of care in human medicine. Experimental spinal cord injury studies in cats have shown that increased lactate levels in spinal cord immediately after injury most likely were attributed to decreased spinal cord perfusion.[41] High doses of MPSS 30 minutes after induced trauma attenuated the secondary injury process dramatically. The intent of high-dose MPSS is to provide adequate tissue concentrations of steroid at the site of injury. The original dose for this regimen was 30 mg/kg IV initially, then a dose of 15 mg/kg given 2 and 6 hours later, followed immediately by a 2.5 mg/kg/hr infusion, which is continued for 42 hours. The total dose of MPSS administered is 165 mg/kg.[43] Recent prospective clinical studies that have used modifications of this protocol have come under intense scrutiny for various reasons, including statistical manipulation, lack of proven efficacy, and increased rates of complications in human beings and dogs.[50-54] Administration of MPSS is time dependent and has shown efficacy if administered within 30 minutes of the injury.[55] Use of high-dose MPSS is not recommended for administration if the time has been longer than 8 hours after sustaining the injury.

Supportive medical management alone is useful if spinal instability is not detected or when there is financial constraint.[56,57] Cats may not tolerate body splints.[56] Strict cage confinement is relied upon for 4 to 6 weeks after the injury to initiate the healing process.[58]

Surgical Management. Surgical management of spinal trauma is recommended in cases of instability or severe spinal cord compression.[58] The timing of surgery relative to the injury is somewhat controversial; however, adequate medical stabilization before surgery is essential. Early decompression has been supported in the laboratory setting in cats, but the optimal time to perform surgery still is unknown.[59] Immediate surgical decompression of the affected site is a controversial subject in human spinal trauma, and some studies have not shown a benefit to early surgery.[60,61]

The technique of surgical stabilization depends somewhat on the fracture type. Decompression alone may be sufficient in some cases in which instability is not present.[45] Decompression was needed in cats that sustained displacement of the intervertebral disc or endplate into the spinal canal.[45] A dorsal laminectomy, preserving the articular processes, suffices for adequate decompression.

Common techniques of internal spinal fixation/stabilization include the use of pins with polymethylmethacrylate and spinal stapling. Spinal stapling involves the use of rigid intramedullary pins that are secured to the spine after reduction of the fracture/luxation. Intramedullary pins are secured to the lamina at the base of the spinous process (Figure 51-4).[62] Spinal stapling is considered technically easier to perform than other described forms of internal stabilization. Limited information

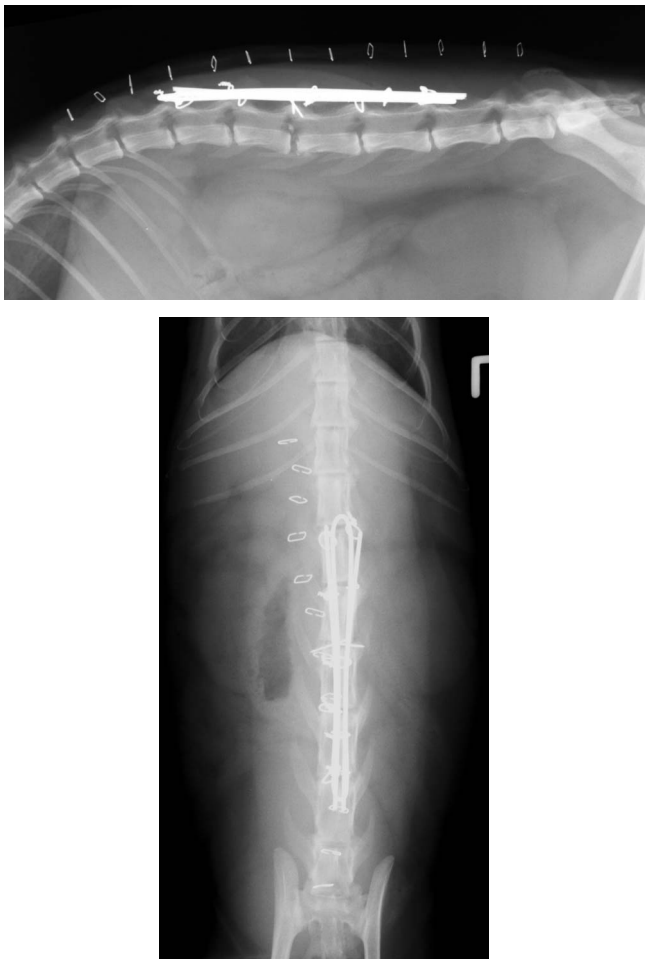


Figure 51-4. A lateral radiograph of the lumbar spine demonstrating use of spinal stapling in a cat with an L3-L4 vertebral subluxation.

is available for the long-term outcome. Problems associated with this type of surgery include fragility of the spinous processes and migration or breakdown of implants.[45] A recent case series involving 16 cats with thoracolumbar trauma described using a figure-8 tension band technique as a modification of spinal stapling.[48] Complications from this technique were not observed.[48]

Successful use of pins and polymethylmethacrylate to stabilize a lumbar fracture in a cat has been described.[63] This form of treatment provides significant stability, particularly for rotational forces.[64] Optimal placement of pins within the vertebral body may be difficult because of the small size of typical feline vertebral bodies. Complications of this procedure include pin migration, pin breakage, pneumothorax, and additional trauma to soft tissue structures.

Outcome for cats with spinal trauma is guarded. Survival rate in one study was only 60 per cent.[46] Cats that did not survive were euthanized or died within 4 days of the injury. Cats with spinal fractures and absence of deep pain perception almost always have a hopeless prognosis. The return of motor function does not equate necessarily with return of voluntary urination.[48]

Spinal Walking: from Laboratory to Clinics. Prognosis for return of voluntary motor function in cases of absent deep pain perception generally is considered grave. However, the cat has been the subject of extensive experimental work studying the return of ambulation after spinalization, or complete transection of the spinal cord. "Spinal walking" is a clinical term used for return of ambulation in an animal with no deep pain perception in the pelvic limbs. In the laboratory setting, this phenomenon is known as spinal locomotion. Pelvic limbs are under no voluntary control, and the thoracic limbs move asynchronously with the pelvic limbs when on a treadmill. Spinal locomotion may be evident within a few days of the injury.[66] The spinal cord generates this pattern of limb movement, which allows for the placement each foot, weight-bearing, and alterations of speed with change in treadmill velocity.[65] The animal also is capable of stepping over objects placed in its way.[66]

Cats have been trained to develop spinal locomotion after complete experimental spinal cord transection at T13. The underlying mechanism may be the result of a spinal locomotor generator.[66] Spinal locomotion is dependent on the development and preparation of a spinal locomotor pattern generator, stimulation of cutaneous receptors, alterations of intraspinal neurochemistry, and input from the midlumbar spinal cord.[66] Plasticity occurs within the spinal cord as a result of training. Lesion location within the spinal cord also can affect the ability to walk; for example, a lesion at the L3-L4 spinal segment is not conducive to development of spinal locomotion.[65]

Spinal walking in a cat with a complete spinal cord injury is much less likely to occur without training.[67] Animals with complete spinal cord transections and no training can begin to take steps within weeks of the injury.[65] Cats with naturally occurring spinal trauma had a low success rate in development of spinal locomotion after injury. Reasons for the low success were attributed to less controlled spinal injury and inadequate physical therapy/training. Training for 30 minutes daily 5 days a week provides an 87 per cent success rate of weight-bearing in the pelvic limbs.[68] Without appropriate rehabilitation the rate drops to 33 per cent.[69]

Variability exists among cats as to when walking movements begin to occur.[66] Repeated training of a cat by placing the thoracic limbs on a nonmoving platform and the pelvic limbs on a treadmill resulted in better walking and weight-bearing ability in the pelvic limbs.[65] This process involves the use of a treadmill, tail support, and various forms of stimulation.[70] Cutaneous stimulation is important for afferent sensory input. Younger animals tend to have a better recovery rate for walking.[66] Training activities resulted in almost all cats regaining the ability to walk. Early intensive training allowed for better walking.[66] Spinal locomotion is maintained only for a finite period after discontinuation of training activities and begins to show decline after 12 weeks.[71]

Long-Term Management of a Deep Pain–Negative Cat. Much has been learned in cats after experimental spinal cord injury regarding optimal medical management of deep pain–negative cats.[70] Bladder expression is required at a minimum of twice daily. Some cats urinate without expression, but the bladder is not emptied completely. Stimulation of the perineum initiates a mass reflex and partial emptying of the bladder.[70] Researchers report that treadmill training also stimulates urination and defecation in cats with complete spinal cord injuries.[70] Inadequate emptying of the bladder predisposes to chronic urinary tract infections[70] (see Chapter 48). Suggestions for care to prevent this problem include adequate bladder expression and water

intake.[70] Chronic bladder infections weaken the muscular wall, further complicating manual emptying of the bladder.[70] Fecal elimination usually can occur without assistance and is aided by perineal stimulation.[70] Diarrhea and constipation still can occur as complications.

Intervertebral Disc Disease

Clinical Presentation and Pathogenesis. Intervertebral disc disease (IVDD) is recognized commonly in cats with approximately 27 published cases.[72] Several case series have been published in recent years.[73-75] The incidence of IVDD as a significant clinical problem compared to other diseases that affect cats has been reported to be 0.12 per cent.[74]

Earlier clinical reports of disc disease in cats were postmortem studies that described cervical and, to a lesser extent, lumbar disc disease in older cats.[76-80] These discs were mostly Hansen type II, with bulging of the annulus fibrosus into the spinal canal, and were described as incidental findings. Characteristics of a degenerated intervertebral disc suggest some degree of chondroid degeneration of the discs.[72] More recent literature describes Hansen type I, with extrusion of nucleus pulposus into the spinal canal, and recognizes this type to be the most common form of disc-related spinal cord compression in cats.[74] IVDD also can occur spontaneously in cats having no history of trauma.[74]

IVDD occurs more frequently in middle to older aged cats. Mean age for all reported cases is 7 years.[72] The age range varies somewhat in different reports, between 3 and 9 years,[73] and 4 and 17 years (mean age of 9.8).[74] No gender or breed predilections exist for IVDD in cats.

Clinical signs of disc disease vary on lesion location and in severity and can consist of back pain and paresis/plegia. Lesion involvement in the thoracolumbar region of the spinal cord is common.[72] Cervical disc disease is uncommon in cats, with two reported cases confirmed by necropsy, and one presumed case diagnosed with MRI.[81-83] Disc spaces between the T11 and L2 vertebrae are affected in 50 per cent of cats with clinical signs of IVDD.[72] The L4-L5 disc interspace also is a common site in 26 per cent of the reported cats with IVDD.[72] IVDD at L7-S1 disc was described in a cat with lower motor neuron signs, flaccid tail, and urinary and fecal incontinence.[84]

Diagnosis. Survey spinal radiographs may reveal typical evidence of disc disease: narrowed disc spaces and evidence of mineralized material in the intervertebral foramen.[74] Collection of CSF is performed to eliminate other potential inflammatory diseases. Findings on CSF analysis in cats with IVDD are not specific and may show a mild neutrophilic pleocytosis and increased protein concentration.

Myelography is used to localize the site of the disc extrusion/herniation more precisely. Computed tomography can detect hyperdense material within the spinal canal at the affected disc space.[74] Findings on MRI suggestive of IVDD include evidence of dehydration of the disc with loss of signal intensity on T2-weighted sequence.[83]

Treatment. Conservative medical management has been used successfully in cats with IVDD; however, in severe spinal cord compression, this form of treatment should not replace surgery. Based on a limited number of case reports, medical management alone may result in a poor outcome.[72] Conservative management still may be a better option in cases with a small amount of extruded disc material in the canal.[83] Medical management usually consists of pain control with use of a combination of narcotics and corticosteroids. Corticosteroid therapy (prednisone 0.5 to 1 mg/kg/day PO) is used short-term in combination with strict cage confinement for 4 to 6 weeks. Physiotherapy also may aid the long-term outcome of neurological function.

Surgical decompression for removal of extruded disc material may be accomplished with use of either a hemilaminectomy or dorsal laminectomy procedure.[73,74] Surgery offers a higher rate of success and more rapid and complete neurological recovery when compared with conservative treatment.[75,85] Many cats still have residual neurological deficits that include paresis and urinary and/or fecal incontinence.[73,74]

Vascular Disorders

Fibrocartilaginous Embolism

Clinical Presentation and Pathogenesis. Fibrocartilaginous embolism (FCE), or embolic myelopathy, has been described in many species including cats (Table 51-1).[86-88] This is a rare disease in cats, with about 7 per cent of spinal cord diseases attributed to vascular causes.[1] In this disease, a small portion of fibrocartilaginous tissue, which is presumed to be intervertebral disc material, occludes the vascular supply to the spinal cord, resulting in an acute onset of asymmetrical spinal cord dysfunction. Typically, FCE is nonprogressive and not painful. Lesions in the cervical and lumbar spinal cord regions have been reported. The mean age from the limited case reports available is 10.2 years, with a range between 8 and 12 years of age.

Diagnosis. Diagnosis of FCE is based on elimination of other causes of myelopathy. CSF analysis may reveal a neutrophilic pleocytosis and an increased protein concentration.[87,88] Similar abnormalities also have been reported with intervertebral disc disease and may simply indicate necrosis.[73,83] Case reports have lacked definitive imaging results, except in one

Table 51-1 | **Published Reports of Fibrocartilaginous Emboli in Cats**

CASE REPORT	BREED/SEX	AGE (YEARS)	LOCATION	SIGNS
Turner et al, 1995[86]	DSH/M	12	Left cervical	Acute left hemiparesis
Zaki et al, 1976*	DSH/FS	10	L6-S3	Acute bilateral paresis
Scott and O'Leary, 1996[88]	DSH/FS	9	L4-S3 Left	Paraplegia
Bichsel et al, 1984†	DSH/unknown	12	Lumbosacral	Paraplegia
Abramson et al, 2002[87]	DSH/MN	8	Left cervical C6-C7	Acute onset ataxia

*Zaki FA, Prata RG, Werner LL: Necrotizing myelopathy in a cat, J Am Vet Med Assoc 169:228-229, 1976.
†Bichsel P, Vandevelde M, Lang J: Spinal cord infarction following fibrocartilaginous embolism in the dog and cat, Schweiz Arch Tierheilkd 126:387-397, 1984.

case in which myelography showed evidence of intramedullary swelling.[88] MR images can be expected to show an increased signal intensity relative to surrounding tissues of the spinal cord parenchyma on a T2-weighted sequence.

Treatment. Treatment strategies have been extrapolated from treatment options recommended in other species with FCE. This consists of high doses of MPSS (if the drug can be administered within 8 hours of the onset of clinical signs), adequate fluid therapy, bladder management, and supportive care. Once the cat is stabilized, physical therapy may aid in recovery. Prognosis in these cases is difficult to predict because the literature in this area shows some bias as definitive diagnosis requires necropsy. Prognosis is presumed guarded to fair in cats that have deep pain perception intact.

Syringomyelia and Hydromyelia

Syringomyelia is an abnormal fluid-filled cavity within the parenchyma of the spinal cord. Hydromyelia often occurs with syringomyelia and is defined as dilation of the central canal. Pathophysiology of syringohydromyelia is associated with alterations in flow of CSF often secondary to a congenital anomaly, infectious disease process, or trauma. Syringohydromyelia has been reported in cats but is not well described.[89] Clinical signs include paraspinal hyperesthesia and paresis. The syrinx can be detected using MRI. Treatment usually is directed toward the underlying cause. An antiinflammatory dose of prednisone (0.5 to 1 mg/kg/day) may reduce edema and inflammatory response.

Spinal Arachnoidal Cysts

Clinical Presentation and Pathogenesis. Diverticulum within the subarachnoid space results in accumulation of CSF and compression of the spinal cord, which causes neurological dysfunction. These diverticula are not true cysts but rather leptomeningeal cavitations that are filled with CSF.[93] Spinal arachnoidal cysts have been reported to cause paresis in cats.[90-93] Another case report documented an intradural epithelial-lined cyst found at the vertebral body of C7 in a 2½-year-old female Burmese cat.[93] Location of these cyst formations is variable in cats and can occur in the cervical, thoracic, and lumbar spine. The cause of arachnoidal cysts is unknown, but may be related to factors that include previous trauma, inflammation, and developmental or congenital malformations.[92] An arachnoidal cyst in a 7-year-old spayed female domestic shorthair cat with paraparesis was associated with a lordotic malalignment of the caudal thoracic spine.[92]

Affected cats usually are young to middle-age with a range between 2 and 7 years of age. Clinical signs usually are chronic and progressive and reflect the location of the cyst. Duration of clinical signs is chronic and progressive in onset. A cat in one report showed signs for only a few weeks.[90]

Diagnosis. Diagnosis of spinal arachnoidal cysts is made using myelography, CT-myelography, or MRI. The diverticulum is identified with myelography as a teardrop shape within the subarachnoid space (Figure 51-5).[92] Magnetic resonance imaging can document a spinal arachnoidal cyst on a T2-weighted sequence as an area of hyperintensity.[93]

Treatment. Reports of treatment protocols for spinal arachnoidal cysts in cats have been limited. Surgical fenestration has been reported.[90,91,93] A hemilaminectomy or dorsal laminectomy is used to expose the cystic structure for dural fenestration and possible excision of the cyst. Outcome in these cases has been excellent with complete recovery. Residual neurological deficits may occur. Histopathology of the cyst wall is recommended to rule out other lesions. Palliative medical management consists of antiinflammatory doses of corticosteroids.

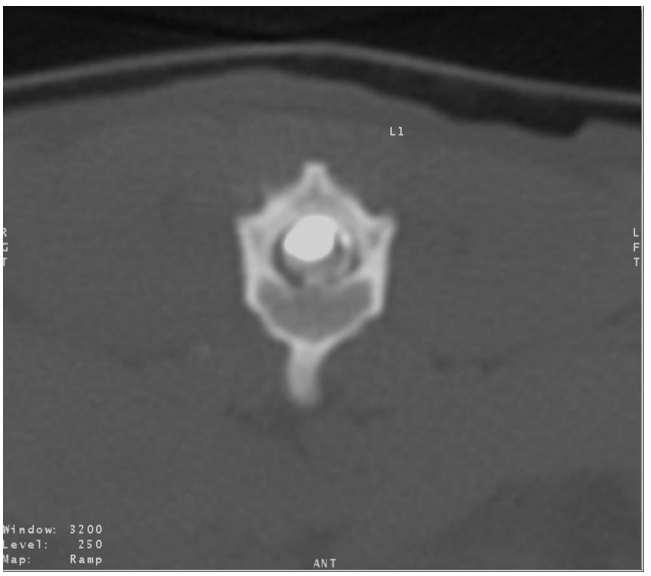


Figure 51-5. An axial CT image after a myelogram of the lumbar spine from a 7-year-old male castrated domestic shorthair cat with a history of progressive upper motor neuron paraparesis. The cat also had a spinal malformation. (Images courtesy Jeryl Jones, Virginia Maryland Regional College of Veterinary Medicine, Blacksburg, Virginia.)

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Chapter 52

Neurogenic Micturition Disorders

Natasha Olby

Successful storage and voiding of urine (micturition) is a complex process dependent on central coordination of autonomic and somatic innervation of the lower urinary tract. Although the most common causes of micturition disorders in cats are not neurological in origin, neurological disturbance of urination can have dire consequences for the patient and must be identified and managed accurately. This chapter reviews the anatomy and physiology of normal micturition in cats and describes how to approach, diagnose, and manage neurogenic micturition disorders. Diseases specific to cats are described in more detail.

ANATOMY AND INNERVATION OF THE LOWER URINARY TRACT

The body, or fundus, of the bladder lies cranial to the point of entry of the ureters and contains the detrusor muscle. The smooth muscle fibers of the detrusor muscle are interlaced in large bundles with no obvious consistent layers in the body of the bladder.[1,2] Individual muscle fibers form an electrical syncytium via gap junctions, which allows smooth propagation of depolarization throughout the muscle. This is an important detail because overdistention of the bladder can disrupt these gap junctions and cause detrusor atony. Therefore management of an animal unable to void urine must involve prevention of bladder wall overdistention.

Distal to the ureters, the smooth muscle of the bladder neck blends with the urethral smooth muscle to form the internal urethral sphincter (Figure 52-1). The internal urethral sphincter is composed of the smooth muscle with inner and outer longitudinal layers and a middle circular layer.[1,2] The outer longitudinal muscle layer is more prominent than the inner layer and decreases in thickness toward the distal urethra. The middle circular layer is larger than both the longitudinal layers and is particularly well developed in the proximal and mid urethral region. The small amount of smooth muscle in the most distal urethra is replaced by the striated muscle of the external urethral sphincter.

The bladder wall and proximal three quarters of the urethra are lined by transitional epithelium. This epithelium is thickest in the bladder neck (five to six cells thick) and thins out in the distal urethra.[1,2] The surface epithelial cells have a much thicker cell membrane than normal and form a permeability barrier that prevents absorption of toxic substances in the urine and allows for storage of concentrated urine without osmotic movement of water. Transitional epithelial cells are connected by interdigitating junctions and can stretch to expand while maintaining a cohesive wall. In the distal urethra, the transitional epithelium is replaced by squamous epithelium.

Innervation of the bladder wall and urethra is provided by the hypogastric, pelvic, and pudendal nerves[3-5] (Figure 52-2). The *hypogastric nerve* carries sympathetic fibers that originate from the intermediate grey matter of the lumbar spinal cord (the second to fifth lumbar segments in cats).[6] The preganglionic neurons synapse in the caudal mesenteric ganglion, and the postganglionic fibers pass to the detrusor muscle and the internal urethral sphincter. Innervation of the detrusor muscle is mediated by β-adrenergic receptors and inhibits detrusor contraction during bladder filling, which allows it to fill smoothly at a constant pressure. The urethral sympathetic receptors are α_1-adrenergic and maintain sphincter tone. The sensitivity of these α_1-adrenergic receptors is enhanced by estrogen acting at local estrogen receptors.[7] Pain caused by extreme distention of the bladder is detected by submucosal sensory nerve endings and mediated via the hypogastric nerve to the lumbar spinal cord.

The *pelvic nerve* carries parasympathetic fibers. The parasympathetic fibers originate in the first to third sacral spinal cord segments and the preganglionic neurons pass from the intermediate grey matter of the spinal cord to synapse either in

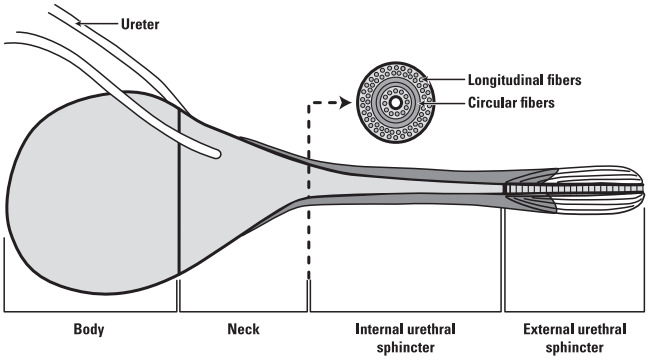


Figure 52-1. Diagram of the feline bladder illustrating the different anatomic areas important in micturition. The inset represents a cross section of the muscle layers in the bladder neck and internal urethral sphincter. The detrusor muscle extends from the body into the neck of the bladder, but the organization of the fibers changes from interlaced bundles with no layering, to three clear layers that are continued into the internal urethral sphincter.

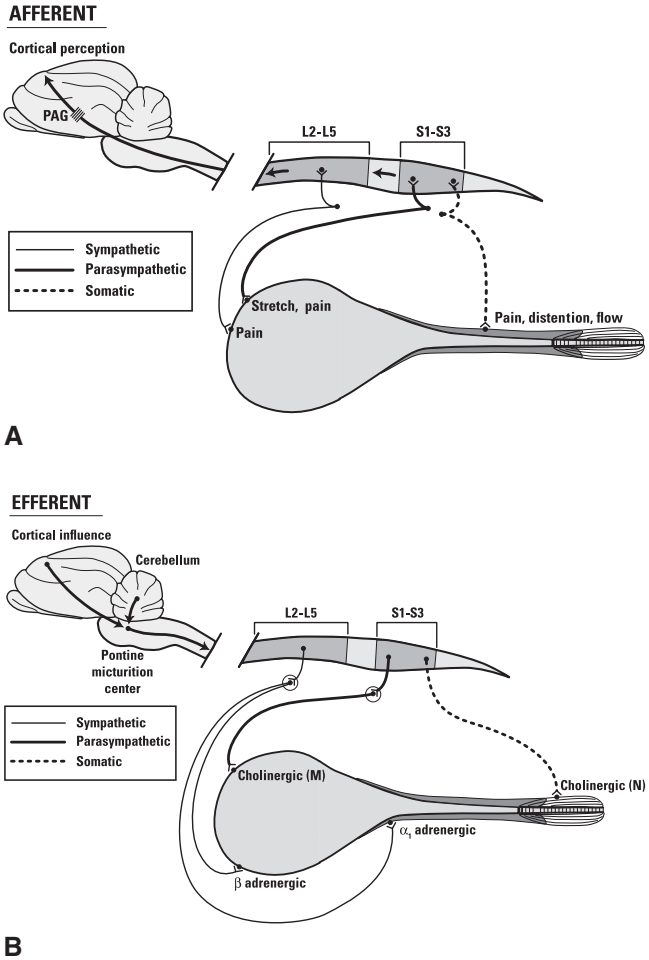


Figure 52-2. Diagramatic representation of the afferent **(A)** and efferent **(B)** pathways important in micturition. *PAG,* Periaqueductal grey matter.

ganglia in the bladder wall or the pelvic plexus. Postganglionic neurons synapse in the detrusor muscle via muscarinic cholinergic receptors. The pelvic nerves also carry sensory information from stretch receptors (and most likely pain receptors) in the bladder wall. These receptors monitor bladder distention and trigger the micturition reflex at a certain threshold. The preganglionic neurons of the parasympathetic and sympathetic nervous systems synapse via nicotinic cholinergic receptors.

Figure 52-3. Diagram illustrating the location of the caudal lumbar and sacral spinal cord segments relative to the vertebral column. *L,* Lumbar; *S,* sacral. Reproduced from Kot et al, 1994, with permission.

The *pudendal nerve* is a somatic nerve that originates from the ventral motor neurons of the sacral spinal cord (the first to third sacral spinal cord segments). It innervates the striated muscle of the external urethral sphincter via nicotinic cholinergic receptors. Sensory innervation of the urethra that detects flow, distention, and pain projects via the pudendal nerve to the sacral spinal cord.

The caudal lumbar and sacral spinal cord segments do not lie directly over their respective vertebrae. The conus medullaris terminates over the body of the first sacral vertebra in more than 80 per cent of cats.[8] The seventh lumbar and first sacral spinal nerves exit over the fifth lumbar vertebra or the junction between the fifth and sixth lumbar vertebrae. The second and third sacral segments lie over the sixth lumbar vertebra or the junction between the sixth and seventh lumbar vertebrae.[8] Each spinal nerve leaves the spinal cord and runs caudally within the spinal canal in the cauda equina to exit from the correct foramen (Figure 52-3).

Central Pathways of Micturition

Successful micturition can occur only if the central pathways also are intact (see Figure 52-2). Afferent pathways project from the sacral spinal cord to the periaqueductal grey matter in the midbrain via the spinothalamic tract and the gracile funiculus,[9] which conveys information on bladder distention. Initiation and coordination of detrusor contraction and sphincter relaxation are controlled by the pontine micturition centers[10] via the reticulospinal and tectospinal tracts. The pontine micturition centers in turn are influenced by the cerebral cortex, the thalamus, the cerebellum, and the basal ganglia to provide full voluntary control of urination.

PHYSIOLOGY OF MICTURITION

The process of micturition can be divided into storage and voiding phases.[5,11]

Storage Phase

Sympathetic innervation takes precedence during the storage phase, mediated largely at the spinal cord level. As the bladder fills, activation of β-adrenergic receptors inhibits the detrusor muscle, which allows the bladder to fill with little change in pressure. The sympathetic nervous system also inhibits the parasympathetic ganglia directly, decreasing parasympathetic input to the detrusor muscle.[3] The muscular arrangement of the urethra and bladder neck allows the urethral sphincter tone to remain higher than intravesical pressure with tonic sympathetic input to the α-adrenergic receptors, which maintains continence during this phase.[12] Additional barriers prevent involuntary micturition when stresses to continence occur. For example, sudden increases in intraabdominal pressure, such as those caused by coughing, are counteracted by a reflex increase in external sphincter tone.[5]

As the bladder distends progressively, the intravesical pressure starts to increase, and a threshold is reached to trigger the micturition reflex. Threshold is detected by stretch receptors in the bladder wall, and the information is conveyed via the pelvic nerves and spinal cord to the periaqueductal grey matter of the midbrain. The threshold for triggering micturition is influenced by the higher components of the micturition pathway and by local factors such as inflammation.

Voiding Phase

This phase is initiated by the pontine micturition centers. In the immediate prevoiding phase, the circular urethral muscle contracts and the longitudinal urethral muscles relax transiently and cause a brief increase in intravesical pressure that precedes the voiding phase.[12] The circular urethral muscle relaxes subsequently and the longitudinal urethral muscles contract, coincident with contraction of the detrusor muscle and relaxation of the external urethral sphincter. Intraabdominal pressure is increased by contraction of the abdominal muscles, and the muscles of the pelvic floor relax, which produces a drop in urethral pressure. In cats, unlike dogs, contraction of the longitudinal muscles of the urethra plays an important role in decreasing urethral pressure. The sensation of urine passing through the urethra reinforces the detrusor muscle contraction, which ensures complete emptying of the bladder.[5]

PATHOPHYSIOLOGY OF NEUROGENIC MICTURITION DYSFUNCTION

Micturition disorders can be categorized functionally as problems voiding urine (urine retention) and problems storing urine (urinary incontinence).[13] They also can be divided neuroanatomically into upper motor neuron (UMN) and lower motor neuron (LMN) categories. However, UMN and LMN bladder dysfunction both can result in the functional problems of urine storage and voiding, reflective of the fact that incontinence occurs whenever urethral pressure drops below that of the bladder. The neuroanatomical localization of micturition dysfunction is based on presence of additional neurological deficits (see below under diagnosis).

The Brain and Micturition Dysfunction

Although the brain is important for normal urination, a lesion within the brain typically does not cause true incontinence or urine retention as a presenting problem. Severe brain stem disease causing stupor or coma may abolish higher control of the micturition reflex, but this usually is not the major presenting problem. Forebrain disease may cause behavioral changes and urination in inappropriate places, generally accompanied by additional signs of forebrain dysfunction (e.g., circling, central blindness). Diseases of the hypothalamic pituitary axis may cause polydipsia and the resulting polyuria may result in inappropriate urination. Cerebellar disease reportedly causes detrusor hyperreactivity (because the cerebellum exerts an inhibitory influence on the detrusor muscle), with urge incontinence. However, I have never seen this sign as a component of cerebellar disease clinically in cats.

Upper Motor Neuron Micturition Dysfunction

UMN urine retention and incontinence occur with spinal cord lesions cranial to the sacral spinal cord segments. Typically the spinal cord lesions are severe enough to cause significant motor and sensory deficits to the pelvic limbs or all four limbs (depending on lesion location). Such lesions result in an increase in detrusor muscle and urethral sphincter tone and activity causing urine retention. Manual expression of the bladder is difficult, but urine still overflows when intravesical pressure exceeds urethral pressure, which tends to occur as the bladder exceeds its capacity and when sudden increases in intraabdominal pressure occur (e.g., when the cat is lifted). Overflow incontinence should not be mistaken for normal urination and always should be suspected when nonambulatory animals urinate when moved.

When complete transection of the suprasacral spinal cord occurs, reflex micturition mediated at a local spinal level usually is reinstated within 1 to 5 weeks.[14] This involuntary urination typically is weak and incomplete, partially because of a failure of coordination of detrusor contraction and urethral sphincter relaxation (detrusor-sphincter or reflex dyssynergia). This results invariably in recurrent urinary tract infections.[15] Most animals recovering from an incomplete suprasacral spinal cord lesion do not establish proper coordination of urethral sphincter relaxation and detrusor contraction immediately, resulting in a period of reflex dyssynergia. This may imply simply a phase through which a cat goes during recovery; however, with a more severe spinal cord lesion, it can be a persistent feature.

Lower Motor Neuron Micturition Disorders

LMN incontinence is caused by dysfunction of the parasympathetic and somatic motor innervation of the bladder and external urethral sphincter. This can result from lesions of the sacral spinal cord segments, nerves of the cauda equina, or peripheral nerves themselves. Such lesions classically produce a large, flaccid bladder that cannot contract and thereby causes urine retention. Decreased external urethral sphincter tone may cause frequent dribbling of urine coincidentally. Fecal

incontinence with a reduced or absent anal reflex and tone often is present. Additional neurological signs depend on the exact location of the lesion.

If incontinence is a result of dysfunction of the autonomic nervous system (dysautonomia, see below for full description), other signs of autonomic dysfunction usually exist, such as mydriasis, vomiting, regurgitation, and keratoconjunctivitis sicca.

With sacral spinal cord or cauda equina lesions, the cat has evidence of involvement of adjacent portions of the central nervous system (CNS) and peripheral nervous system (PNS). An example is in a cat with a tail injury. It still may be ambulatory (as the femoral nerve is spared) but may have sciatic nerve deficits (plantigrade stance, decreased hock flexion on withdrawal reflexes). Such lesions spare the sympathetic innervation of the bladder, and the internal urethral sphincter may maintain normal tone, which makes the bladder difficult to express in a proportion of cases. Additionally, sensory feedback (via the pelvic nerves) that initiates the micturition reflex is affected, and so the trigger for relaxation of the urethral sphincters is lost. As a result, the bladder is difficult to express; this is a common source of confusion that leads to misinterpretation of the signs and inaccurate localization of the neurological lesion. Increased urethral tone is encountered more frequently in cats than in dogs, which perhaps reflects the importance of contraction of the longitudinal muscles of the bladder neck and proximal urethra to decrease urethral tone. As pain is mediated via the hypogastric nerve, cats may exhibit a painful response upon bladder palpation and expression and may appear to strain during urination.

Functional Urethral Obstruction (Detrusor-Sphincter Dyssynergia or Reflex Dyssynergia)

Failure to coordinate detrusor contraction and urethral sphincter relaxation is a common component of UMN and LMN micturition disorders.[16,17] Affected animals are unable to produce or maintain an adequate stream of urine in spite of detrusor contraction. Although several case reports exist of idiopathic functional urethral obstruction in dogs, no such reports exist for cats. However, chronic functional urethral obstruction in cats after traumatic injury to the sacral and coccygeal vertebrae has been reported.[17] A presumptive diagnosis is made by excluding anatomical obstruction, but a definitive diagnosis can be made only by performance of urodynamic studies (see below). The most common cause of urethral obstruction in cats is anatomical obstruction resulting from urethral inflammation, urolithiasis, urethral stricture, or neoplasm. These causes must be ruled out before a diagnosis of idiopathic functional urethral obstruction is made.

DIAGNOSTIC APPROACH TO THE INCONTINENT CAT

Investigation of urinary incontinence begins by obtaining an accurate history and performing careful physical and neurological examinations. The history should allow the clinician to ascertain whether the problem is true incontinence rather than inappropriate urination and to establish the presence of additional neurological signs. The physical examination always should include palpation of the bladder (before and after voluntary voiding), observation of urination, and attempts at manual bladder expression. The residual volume of urine following voiding should be measured and should not exceed 0.2 to 0.4 ml/kg body weight.[11] Particular points to note are the ease of producing and maintaining a stream of urine, presence of pain associated with urination, and dribbling after apparent completion of voiding.

In the case of neurogenic micturition disorders, with few exceptions (e.g., idiopathic functional urethral obstruction), additional neurological deficits should indicate that nervous system abnormalities underlie the problem. These deficits can be categorized according to the localization of the problem: UMN spinal cord disease (lesions cranial to the sacral spinal cord); LMN spinal cord and cauda equina disease; and dysautonomia.

The associated abnormal neurological examination findings in each case are summarized in Table 52-1.

The diagnostic approach depends on the neuroanatomical localization but always should include a urinalysis and urine culture because urinary tract infections are common secondary complications. Other conditions can complicate the clinical picture and mimic neurogenic micturition dysfunction. Urolithiasis can cause difficulty in voiding, often associated

Table 52-1 | **A Summary of the Neurological Signs Present with Lesions in Different Parts of the Nervous System**

LOCALIZATION	MOTOR FUNCTION	CP/POSTURAL REACTIONS	SPINAL REFLEXES	OTHER SIGNS
C1-C5	Nonambulatory tetraparesis/plegia	TL: +-0 PL: +-0	TL: ++-+++ PL: ++-+++	
C6-T2	Nonambulatory tetraparesis/plegia	TL: +-0 PL: +-0	TL: 0-+ PL: ++-+++	
T3-L3	Nonambulatory paraparesis/plegia	TL: ++ PL: +-0	TL: ++ PL: ++-+++	May have cutaneous trunci reflex cut off
L4-L6	Nonambulatory paraparesis/plegia	TL: ++ PL: +-0	TL: ++ PL: femoral: 0-+ sciatic: ++-+++	
L7-S3 and cauda equina	Normal or ambulatory paraparesis	TL: ++ PL: 0-++	TL: ++ PL: femoral: ++ sciatic: 0-++	Tail: paretic/plegic + decreased tone Anal reflex: 0-+
Generalized LMN (dysautonomia)	Normal	Normal	Normal	KCS; mydriasis; vomiting; regurgitation; constipation

C, Cervical; *T,* thoracic; *L,* lumbar; *S,* sacral; *TL,* thoracic limbs; *PL,* pelvic limbs; *KCS,* keratoconjunctivitis sicca; 0, absent; +, decreased; ++, normal; +++, increased.

with dribbling of urine after attempts to void and when the animal is relaxed. If the bladder cannot be expressed manually, a catheter must be passed using sterile technique to ensure no anatomical reason exists for urethral obstruction. If a physical obstruction is encountered, a diagnostic evaluation of the lower urinary tract (contrast radiography, ultrasonography)[18] should be undertaken before pursuing neurological causes for the problem. Serum biochemistry panel, complete blood cell count, and blood tests for feline leukemia virus and feline immunodeficiency virus are indicated in the majority of cases. Thoracic and abdominal radiography and ultrasound are indicated in all cats for which neoplasia or dysautonomia are suspected. Survey spinal radiographs are indicated when the lesion is localized to the spinal cord or the cauda equina. Advanced imaging of the spinal cord and cauda equina (myelography +/– computed tomography [CT], epidurography, or magnetic resonance imaging [MRI]) is indicated dependent on neuroanatomical localization and presence or absence of abnormalities on survey spinal radiographs. MRI is the preferred imaging technique because it is the least invasive test available and it provides the most anatomical detail for soft tissue structures. Cerebrospinal fluid (CSF) analysis should be performed in any cat with spinal cord disease. Specific tests to evaluate autonomic dysfunction are described in more detail in discussion of dysautonomia.

Urodynamic testing for the lower urinary tract is possible, although difficult to perform in cats. Cystometrography measures the bladder pressure during the storage and voiding phases of micturition.[11] Urethral pressure profilometry determines the pressure along the length of the urethra, which provides information on the maximum urethral pressure, the functional length of the urethra, and focal sites of increased or decreased pressure.[11,13,19] Measurements are made by withdrawing a catheter connected to a pressure transducer along the length of the urethra. The catheter can be perfused with isotonic saline at a constant rate during the procedure, or a specialized catheter containing micropressure transducers can be used. Measurements are affected by sedation, but performance of this type of study in cats without the benefit of chemical restraint is difficult.[20] Electromyography of the external anal sphincter can be used to confirm LMN denervation resulting from pudendal nerve dysfunction. In the majority of cases, urodynamic testing is not necessary; however, this type of functional testing becomes important in the absence of other neurological deficits and when a definitive diagnosis has not been reached.

MANAGEMENT OF NEUROGENIC MICTURITION DYSFUNCTION

Specific therapies for different diseases are described below under each disease. However, basic therapeutic steps must be taken in all cases. Decisions on choice of pharmacological treatment for neurogenic micturition disorders are based on determining whether tone of the urethral sphincters and detrusor muscle is increased or decreased.

Increased Urethral Tone with Increased or Decreased Detrusor Tone

Increased urethral tone results in urine retention and occurs with UMN micturition disorders, LMN micturition disorders with excess sympathetic tone, and idiopathic functional urethral obstruction. The bladder must not become overdistended, which results in damage to the detrusor muscle and secondary detrusor atony. In my experience, severe hematuria develops commonly within 24 to 48 hours in cats in which the bladder has become overdistended. This resolves rapidly once the bladder is kept empty. To avoid these complications, the bladder should be expressed manually three to four times a day.

If manual expression is not possible, the bladder should be catheterized. Ideally an indwelling catheter is not placed because this predisposes to infection.[21] Sterile intermittent catheterization of male cats twice daily is possible for a limited period of time but is not possible in female cats. Transurethral indwelling catheters can be placed for limited periods but should be attached to a sterile, closed urine collection system. If this approach is taken in male cats, a soft catheter should be used rather than the stiffer "tom cat" catheter (made of polypropylene) to avoid damaging the bladder wall. If catheterization is needed for more than a week, a tube cystostomy should be placed.[22] Tube cystostomies can provide a long-term solution for some chronically affected cats, lasting months and even years if managed carefully.

Manual expression can be aided by pharmacological relaxation of the urethral sphincters (see Table 62-2). α-Adrenergic antagonists (e.g., phenoxybenzamine, prazosin) can be administered to relax the internal urethral sphincter, and diazepam may help to relax the external urethral sphincter. However, oral diazepam can cause an idiosyncratic hepatic necrosis in a small proportion of cats. Dantrolene has been used as an alternative to diazepam but also is associated with adverse side effects.

Antibiotics should not be administered as a prophylactic measure because this simply encourages the growth of antibiotic-resistant bacteria. Instead, urine should be monitored daily with a dipstick to check for the presence of protein and blood, and antibiotics administered when an infection develops based on the results of a urine culture. In the case of an obvious urinary tract infection, a broad-spectrum antibiotic such as cephalexin or amoxicillin/clavulanic acid can be administered while the results of culture and sensitivity tests are determined (see Chapter 48).

It is common practice to administer a cholinergic agonist such as bethanechol chloride (Table 52-2) to promote detrusor contraction. However, this is not advisable if the bladder is not easily expressible, because it simply makes the detrusor muscle contract against closed urethral sphincters, causing discomfort and potentially causing reflux of urine up the ureters. An α-antagonist should be administered first to counteract the nonspecific cholinergic action of bethanechol on the presynaptic cholinergic neurons of the hypogastric nerve, which can further increase urethral sphincter tone.

Decreased Urethral and Detrusor Tone

Decreased urethral tone results in incontinence. This problem is compounded by decreased detrusor tone, because incomplete (or absent) voiding produces a reservoir of urine that leaks whenever intravesical pressure exceeds urethral pressure. Therefore the incontinence seen with these LMN neurological disorders is much more severe than that encountered with urethral sphincter mechanism incontinence. Whenever the intravesical pressure exceeds that of the urethra, urine overflow occurs. Urine leakage therefore does not imply decreased urethral tone automatically but simply can reflect very high

Table 52-2 | **Summary of the Drugs That Can Be Used to Alter the Function of the Detrusor Muscle and the Urethral Sphincters**

DRUG	TARGET	ACTION	DOSE	SIDE EFFECTS/*CI*
DECREASE URETHRAL TONE				
Phenoxybenzamine (Dibenzyline)	Internal urethral sphincter	α-adrenergic antagonist	0.25-0.5 mg/kg PO q12-24h	Hypotension, tachycardia/*cardiac disease, renal failure, diabetes mellitus, glaucoma*
Prazosin	Internal urethral sphincter	α-adrenergic antagonist	0.25-0.5 mg PO q12-24h	As for phenoxybenzamine
Diazepam (Valium)	External urethral sphincter	Centrally acting skeletal muscle relaxant	0.25-0.5 mg/kg PO q8-12h	Sedation, polyphagia, hepatotoxicity paradoxical excitement/*hepatic disease*
Dantrolene	External urethral sphincter	Skeletal muscle relaxant	0.5-2 mg/kg PO q8h	Weakness, hepatotoxicity, sedation, GI upset/*cardiopulmonary disease*
INCREASE DETRUSOR CONTRACTILITY				
Bethanechol chloride (Urecholine)	Detrusor muscle	Parasympathomimetic	1.25-5 mg/cat PO q8-12h	Ptyalism, vomiting, diarrhea/*urethral obstruction, GI disease*
Cisapride	Detrusor muscle	Increase ACh release	1.25-5 mg/cat PO q8-12h	Diarrhea/*decrease dose with hepatic failure*

Contraindications (CI) are listed in italics in the last column.
PO, Per os; ACh, acetylcholine

Table 52-3 | **Diseases* That Can Cause Neurogenic Micturition Disorders in Cats**

DISEASE CLASS	DISEASE	DIAGNOSTIC TEST
Degenerative	**IVDD**	Myelography, CT, or MRI
Anomalous	**Sacrocaudal dysgenesis**	Spinal radiographs, MRI
	Subarachnoid cysts	Myelography or MRI
Neoplastic	Vertebral neoplasms Round cell tumors Primary CNS tumors Nerve sheath tumors	Spinal radiographs, myelography, CT, or MRI; biopsy to establish definitive diagnosis
Infectious, inflammatory	FeLV/FIV myelopathy	Serum tests for FeLV and FIV, rule out other diseases CSF analysis
	FIP	Elevated serum globulins, CSF antibody titers and cytology, elevated CSF protein, neutrophilic pleocytosis, hydrocephalus
	Cryptococcus	CSF antigen titers and cytology
	Bacterial discospondylitis	Survey spinal radiographs, urine, blood or disc aspirate cultures
	Epidural abscess	CT or MRI, cytology and culture
Idiopathic	Functional urethral obstruction	Rule out of other diseases (lower urinary tract workup) Urodynamic studies
	Dysautonomia	Presence of generalized signs of autonomic dysfunction, reduced urinary catecholamines
Trauma	**Sacrocaudal injury**	Spinal radiographs, CT, or MRI
Vascular	FCE	MRI
	Bleeding disorder	Coagulation tests
	Infarct	MRI, angiography

CT, Computed tomography; *FCE,* fibrocartilaginous embolism; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency virus; *FIP,* feline infectious peritonitis; *MRI,* magnetic resonance imaging.
*The disorders in **boldface** type are covered in detail in the chapter.

intravesical pressure. A full neurological examination should always be performed to localize the lesion correctly. As for UMN lesions, the bladder must not become overdistended, and regular bladder expression should be undertaken. This also helps to minimize persistent dribbling of urine and associated urine scald. However, in contrast to UMN lesions, urethral pressure usually is low, and the main obstacle to complete bladder expression is the lack of tone to the detrusor muscle. Treatment for urine scald is to clean and dry the affected skin carefully and apply a barrier cream. If fecal incontinence also is present, the perineum and tail must be kept clean. Lack of urethral tone predisposes affected cats to bladder infections. These should be treated as for UMN micturition disorders. Bethanechol chloride can be administered to increase detrusor activity if the bladder is easily expressible (see Table 52-2). Although it would seem intuitive to administer an α-adrenergic agonist such as phenylpropanolamine to increase urethral sphincter tone, clinical improvement of incontinence may not seem evident.

DISORDERS OF NEUROGENIC MICTURITION

Because any spinal cord disease severe enough to cause paralysis can cause micturition dysfunction, these diseases are not be considered individually, although a list of common disorders and the diagnostic tests indicated is provided in Table 52-3. Instead, diseases important in cats in which urinary dysfunction is a prominent feature are described.

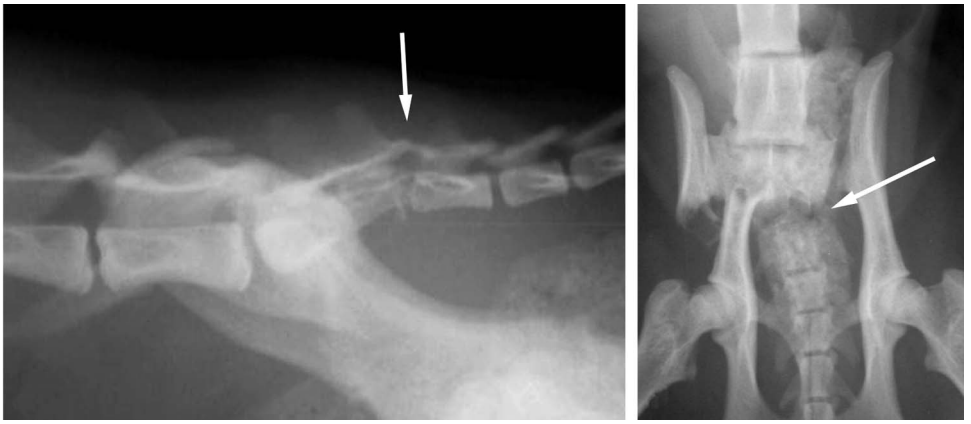


Figure 52-4. Lateral **(A)** and ventrodorsal **(B)** radiographs of the lumbosacral spine and pelvis of a 4-year-old male castrated cat. Note luxation of the sacrocaudal vertebrae *(arrows)* and a fracture of the right ileum. The cat returned home after being missing overnight. No other external evidence of trauma existed. Presenting signs included paralysis of the tail with loss of pain perception, urine retention with an easily expressible bladder, absent anal tone with loss of perineal sensation, and reduced hock flexion in the right pelvic limb. Perineal sensation returned 2 weeks after presentation, and the cat started to urinate on its own 1 week later.

Sacrocaudal (Sacrococcygeal) Injuries

Presenting Signs and Pathogenesis

Cats are prone to injuries to the sacrocaudal vertebrae and associated soft tissues as a result of trauma and cat bites. Frequently these injuries result in obvious physical abnormalities such as a caudal vertebral luxation or a degloving injury to the tail. However, sometimes external evidence of a traumatic episode is not obvious. Nevertheless, these injuries cause damage to the cauda equina, either by direct compression from displaced sacral and/or caudal vertebral fractures and luxations (Figure 52-4), or by a traction injury to the cauda equina, or by development of an epidural abscess (in the case of bites).

Specific structures often are involved with trauma to the sacrocaudal region of the spine, for example, the caudal (coccygeal) nerves innervating the tail. This causes paresis or paralysis of the tail (usually with decreased tone) with or without loss of pain perception in the distal tail. The pudendal nerve provides motor innervation of the external anal and urethral sphincters, and sensory innervation of the perineal region extending to the caudomedial surface of the thigh. Pudendal nerve injury can cause loss of the perineal reflex and perineal sensation and decreased anal tone and external urethral tone, which potentially results in urinary and fecal incontinence. Injury to the pelvic nerve results in atony and paralysis of the detrusor muscle, which makes voiding of urine difficult. Sensory feedback from bladder wall distention that normally triggers the micturition reflex also is lost, although pain perception from a full bladder still can be conveyed by the intact hypogastric nerves. If the lesion is locally extensive, the sciatic nerves can be affected, which causes difficulty rising, a plantigrade stance and gait, and decreased or absent hock flexion when testing the withdrawal reflexes. If the lesion is severe enough, deep pain perception may be lost to the lateral digits.

Diagnosis

If history of trauma is known or obvious external signs of injury are present, these cases do not pose a diagnostic problem. However, in about 20 per cent of cases, obvious clues may be lacking.[23] On physical examination, the sacrocaudal region of the spine usually is hyperesthetic, and a luxation or fracture of the caudal vertebrae or the sacrocaudal junction may be palpable. Spinal radiographs demonstrate the presence of fractures and luxations (see Figure 52-4), and these can be delineated further with CT or MRI. In the absence of abnormalities on survey spinal radiographs, MRI may identify edema or hemorrhage around the cauda equina supportive of the diagnosis. The presence of a soft tissue density within the vertebral canal, particularly if associated with cellulitis and puncture wounds on the skin, is evidence for the presence of a cat bite abscess.

Treatment

Treatment of cats with these injuries focuses on correct management of the lower urinary tract (see above) while the patient recovers neurological function. Further damage to the bladder that may prevent a full recovery should be avoided. Therefore in patients in which manual expression of the bladder is not possible, bladder catheterization (transurethral or tube cystostomy) may be necessary. Amputation of the tail is indicated if it is paralyzed irreversibly (determined by the presence of a luxation in association with loss of pain perception in the tail). Although tail amputation may make a cat more prone to fall when in precarious situations,[24] it should not affect the cat's quality of life adversely. If sensory perception to the tail is intact, the tail should recover motor function with no therapeutic intervention unless the presence of an unstable fracture or luxation causes further clinical deterioration. Ongoing compression of the cauda equina can be alleviated by a dorsal laminectomy, and in rare instances, spinal stabilization may be appropriate. Epidural abscesses can be treated by laminectomy and flushing of the epidural space followed by systemic administration of appropriate antibiotics.

Prognosis

Recovery of normal continence often poses a significant problem in these cases, and the owners must understand the potential for long-term fecal and urinary incontinence. Recov-

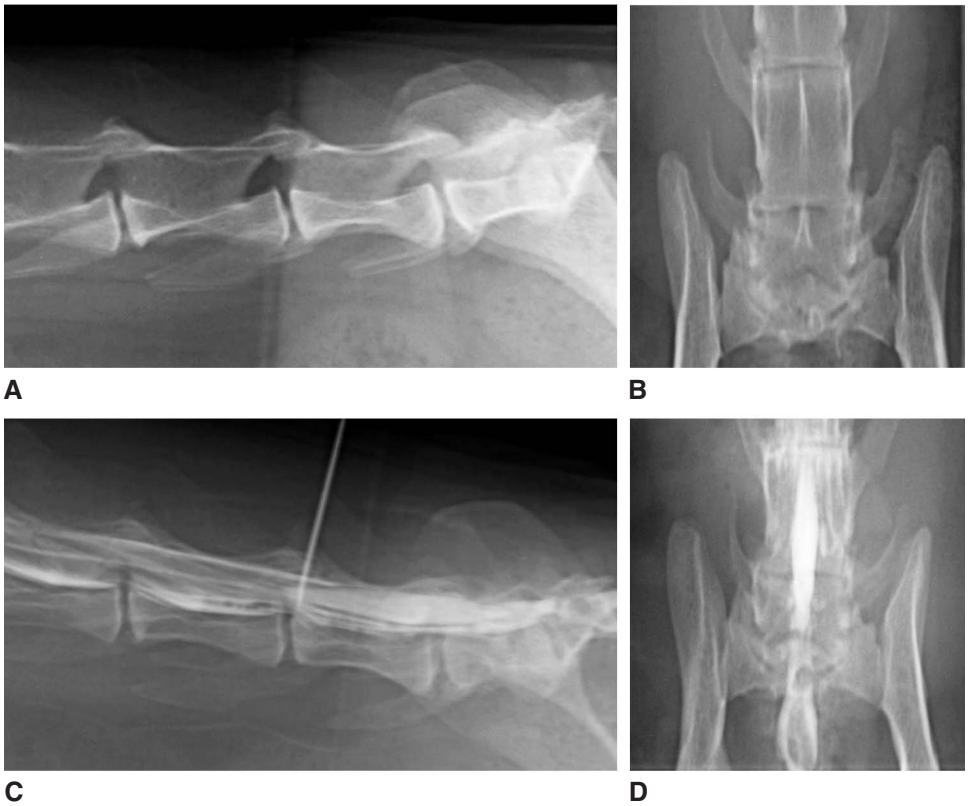


Figure 52-5. Sacrocaudal dysgenesis in a 14-year-old cat. **A** and **B** are lateral and ventrodorsal projections of the lumbar and sacral spine. The sacrum is reduced in size dramatically. **C** and **D** are lateral and ventrodorsal images of the myelogram. A large syrinx filled with contrast medium can be seen extending over sixth and seventh lumbar vertebrae and into the sacral region. Contrast medium also has leaked epidurally, although it is unclear whether this occurred as a result of direct injection into the epidural space or as a result of a communication between the epidural and subarachnoid spaces. This cat did not have any neurological deficits until 14 years of age.

ery of ambulation does not imply recovery of normal micturition. One study has looked at the long-term outcome of cats with these injuries. The most useful parameter to assess is the presence of perineal sensation (because this reflects the integrity of the pudendal nerves, and by implication the pelvic nerves resulting from their common source in the spinal cord).[23] The presence of perineal sensation at the time of presentation is a good prognostic sign. Absence of perineal sensation does not imply that the cat cannot recover, but persistent absence of perineal sensation 1 month after injury carries an extremely guarded prognosis for recovery of continence.[23] Clearly, if evidence exists on MRIs or at surgery of complete disruption of the sacral nerves, the prognosis for recovery of continence is extremely guarded.

Sacrocaudal (Sacrococcygeal) Dysgenesis

Presenting Signs and Pathogenesis

So-called tailless (Manx) cats originated in the Isle of Man and now they are distributed worldwide. Selective breeding for the tailless phenotype has resulted in congenital malformations of the caudal lumbar, sacral and caudal vertebrae, and spinal cord. The condition is inherited in Manx cats by an autosomal dominant trait that has incomplete penetrance, other unidentified modifying genes, or variable expressivity, producing a range of phenotypes.[25-27] Breeding studies have shown a variety of phenotypes,[25] including the following:

- The *rumpy* cat with no caudal vertebrae and therefore truly tailless. Fifty per cent of this phenotype suffer from urinary incontinence[26]
- The *rumpy-riser* with several caudal vertebrae (1 to 7) fused together in an upright position
- The *stumpy* cat with several caudal vertebrae (2 to 14 vertebrae), some of which are malformed, causing a kink
- The normal cat

Essentially, these cats have spina bifida, a term that refers to a group of developmental defects with failure of fusion of vertebral arches with or without protrusion and dysplasia of the spinal cord and/or the meninges. Complete agenesis or dysgenesis of the caudal lumbar, sacral, and caudal vertebrae may occur (Figure 52-5). The meninges alone or the meninges and spinal cord may protrude through the bone deficit (meningoceles and meningomyeloceles). Failure of fusion of the sacrocaudal spinal cord can manifest as spinal dysraphism (myelodysplasia), defects of the central canal, myeloschisis (cleft spinal cord), and abnormalities of the cauda equina such as tethering.[28] Affected cats frequently have syringohydromyelia that may extend cranially to other regions of the spinal cord, causing more neurological dysfunction (see Figure 52-5).

Affected Manx cats have been studied extensively as a model of spinal malformations, and detailed information is

available on the electrophysiological and histopathological features of this disease.[25-30] The detrusor muscle is reported to be areflexic, the tone of the proximal urethra is altered, and electromyographic activity in the muscles of the pelvic floor are abnormal. Contrary to expectations, one group also reported a complete absence of adrenergic innervation of the bladder and urethra, whereas the cholinergic innervation was normal.[26]

Clinical signs usually are evident soon after birth. Typically clinical signs are static but can be progressive if hydromyelia or syringomyelia develops as a result of continued accumulation of CSF within the spinal cord. More rarely, signs develop much later in life as was the case of the cat illustrated in Figure 52-5. The signs reflect involvement of the caudal lumbar and sacral spinal cord segments predominantly causing a plantigrade stance, and fecal and urinary incontinence. In rare instances, the development of syringohydromyelia can affect the spinal cord further cranially and cause paraplegia.

Diagnosis

Diagnosis is suspected with consistent clinical signs in a Manx cat. Vertebral malformations can be confirmed by survey spinal radiography and further delineated by computed tomography, whereas the spinal cord malformations can be identified most effectively on MRI. Myelography sometimes may highlight the spinal cord malformations (see Figure 52-5) but is not recommended because it has a high chance of causing clinical deterioration and may fail to identify syringohydromyelia.

Treatment and Prognosis

Treatment centers on management of the incontinence and prognosis is poor. Abnormalities such as meningoceles and tethered cauda equina can be addressed surgically to prevent progression,[28] but an improvement in function is unlikely.

Feline Dysautonomia

Presenting Signs and Pathogenesis

Primary dysautonomias are enigmatic diseases in which widespread degeneration of the autonomic nervous system occurs. Feline dysautonomia was first described by Key and Gaskell in the early 1980s after outbreaks of the disease in the United Kingdom. The disease therefore is sometimes referred to as Key Gaskell disease. Over the next decade, widespread reports of the disease existed in the United Kingdom[31,32] and Scandinavia.[33] After 1986, outbreaks decreased in frequency, but individual cases still occur worldwide,[34] and occasional outbreaks are reported.[35] Histologically, widespread neuronal degeneration exists in autonomic ganglia[31] and until recently, epidemiological and clinical studies have failed to identify the cause of the disease. Although nearly 50 per cent of affected cats came from multicat households in the reports dating from the 1980s, in the majority of these incidents, only single cats from the households were affected. Moreover, when more than one cat was affected, they were often related, which suggests a genetic predisposition. A more recent proposal states that the disease results from infection with *Clostridium botulinum* type C.[36] Clostridial toxin was detected in the dry food, feces, and ileal contents of affected cats from one household, and levels of IgA antibodies to *C. botulinum* type C and its toxin were significantly higher in the feces of affected cats when compared with healthy controls.

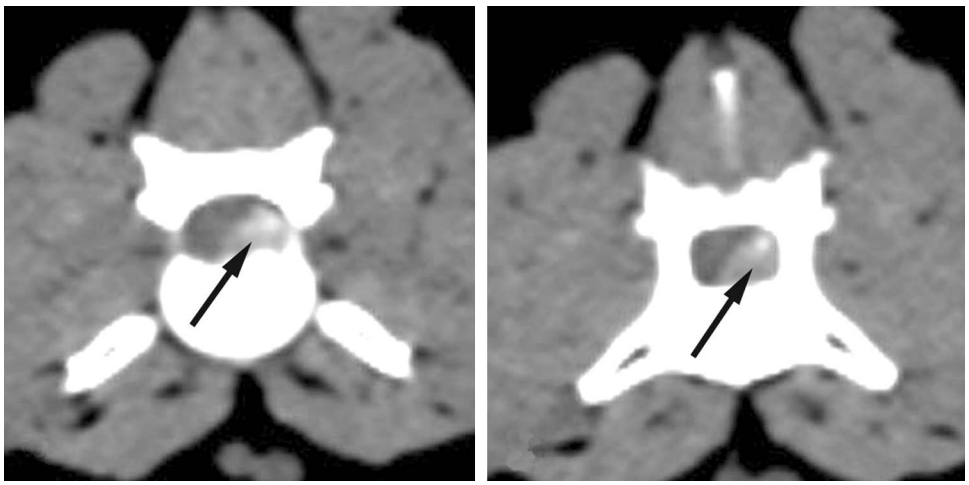
Clinically, cats can present at any age with a wide array of different signs reflecting autonomic dysfunction. Parasympathetic signs often predominate and include mydriasis, reduced tear production, xerostomia, dry mucous membranes, megaesophagus with regurgitation and vomiting, ileus, constipation, and urine retention. Sympathetic signs include bradycardia and prolapsed nictitans. The initial signs often are depression and anorexia, followed by development of more obvious autonomic dysfunction. Pupil dilation often occurs within 3 days and is a consistent sign. The course of the disease depends on the severity of signs and can be rapid; severely affected cats die or are euthanized within 1 to 2 weeks of onset of signs.

Diagnosis

The presenting clinical signs of generalized autonomic dysfunction should alert the veterinarian to the possible diagnosis. Routine blood work often is unremarkable (depending on the presence of secondary systemic diseases such as aspiration pneumonia). Reduced tear production can be confirmed by performing a Schirmer tear test, and the presence of megaesophagus, constipation, and urine retention can be identified on survey radiographs of the thorax and abdomen. Esophageal dysmotility can be confirmed by fluoroscopic contrast esophography, although this should not be performed in cases of obvious esophageal dilation because of the risk of aspiration. Interestingly, abnormal esophageal motility was detected using contrast esophography in two apparently normal cats from the same household in which six other cats developed the disease, which suggests that subclinical disease can be present. Urinary catecholamine excretion can be quantified over 24 hours[34] and is markedly decreased in affected cats. Mydriasis is corrected by topical administration of pilocarpine (0.1 per cent), and the protruded third eyelids should retract after topical administration of epinephrine (1:10,000). Definitive diagnosis is reached by histopathological findings at necropsy.

Treatment and Prognosis

This disease carries a poor prognosis: only 25 to 50 per cent of affected cats survive. Poor prognostic indicators include the presence of bradycardia,[35] generalized severe megaesophagus, and failure to respond to supportive therapy within 10 days.[31,32] Treatment is aimed at addressing autonomic dysfunction pharmacologically and providing supportive care. Constipation and urine retention can be treated by administration of bethanechol chloride, although mildly affected animals may develop diarrhea as a side effect, which necessitates discontinuation of the drug. Gastrointestinal motility may be aided by cisapride and metaclopramide, and pupil dilation should resolve with topical administration of pilocarpine hydrochloride. Artificial tears should be placed topically in cats with reduced tear production. Supportive care includes intravenous administration of fluids in dehydrated animals and parenteral feeding if necessary (see Chapter 16). In less severely affected animals, regurgitation may be prevented by feeding from a height. Recovery may be extremely protracted (over a year) in animals that survive.



A B

Figure 52-6. Computed tomographic images of the lumbar spine showing herniated disc material at the fifth and sixth lumbar intervertebral disc space in a 10-year-old male castrated cat. The *arrows* indicate the herniated disc material within the vertebral canal. Onset of signs was associated with jumping up onto a table. At presentation, the cat was paraplegic with reduced patellar and withdrawal reflexes and perineal reflex. The tail was paralyzed with loss of pain perception. Additionally, loss of pain perception occurred in both pelvic limbs and the perineum. The cat was unable to void urine and his bladder was difficult to express manually. Herniated disc material was removed via a hemilaminectomy. The following day the cat had recovered pain perception and he was able to ambulate within 7 days. Manual expression of his bladder was possible after initiation of treatment with phenoxybenzamine, and voluntary voiding occurred within 2 weeks. The cat made a complete recovery over a period of 6 weeks.

Caudal Lumbar Intervertebral Disc Herniations

Pathogenesis and Presenting Signs

Intervertebral disc herniations are a common cause of spinal cord injury and incontinence in dogs but are recognized less commonly in cats (see Chapter 51). However, cats can suffer acute intervertebral disc herniations[37,38] and older, overweight cats tend to herniate discs in their caudal lumbar spine (the fifth lumbar to first sacral vertebra) (Figure 52-6).[38] In my experience, these cats can recover motor function quickly but may have persistent problems with urine retention resulting from the damage to the sacral spinal cord segments and therefore deserve a mention in this chapter.

Diagnosis

Intervertebral disc herniations should be a differential diagnosis in cases of acute onset of neurological signs and pain that localize to the caudal lumbar or lumbosacral spinal cord. Survey spinal radiographs may reveal the presence of mineralized intervertebral disc material in the vertebral canal, narrowing of intervertebral disc spaces, and a change in opacification of the intervertebral foramen suggestive of a disc herniation. Definitive diagnosis is reached by advanced imaging of the lumbar and lumbosacral spine (see Figure 52-6).

Treatment and Prognosis

Treatment includes surgical decompression of the spinal cord and cauda equina by removal of herniated disc material via a laminectomy or hemilaminectomy. Increased internal urethral sphincter tone tends to be a prominent feature in these cats, which together with decreased detrusor tone can make bladder expression very difficult. In such cases, treatment with urethral muscle relaxants (see Table 52-2) and catheterization often is necessary. Prognosis for the recovery of motor function is excellent because the femoral nerve usually is spared. Prognosis for return of normal micturition can be determined by evaluation of perineal sensation, as for sacrocaudal injuries.

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Chapter 53

Miscellaneous Encephalopathies

Beverly K. Sturges and Peter J. Dickinson

Several unusual encephalopathies are presented in this chapter that may be encountered in feline medicine. Although most of these diseases cause signs of marked, progressive neurological dysfunction that reflect the anatomical localization with the central nervous system (CNS), prognosis varies considerably, depending on the underlying etiology and pathophysiology. A definitive diagnosis, made in a timely fashion, is essential whenever possible to determine appropriate treatment and to ensure the best possible outcome for the patient.

OTOGENIC INTRACRANIAL INFECTION

Etiology

Extension of otitis media/interna into the CNS is a serious complication that may occur in cats of any age, breed, or sex.[1-3] The apparently low incidence of intracranial spread of ear disease in cats may contribute to decreased recognition of the neurological signs. Most intracranial complications originate from subacute to chronic ear infections, resulting in abscess formation in the brain.[2,4-7] Intracranial extension of acute otitis media/interna is more likely to cause severe, diffuse meningitis.[5,7,8]

Clinical Signs

Affected cats have brainstem dysfunction that includes vestibular signs, mentation changes, and ataxia. In cats with a peracute/acute onset, clinical signs of vestibular dysfunction may be marked and progressive, with intermittent opisthotonic posturing, and rapidly declining mental state (obtunded to stuporous or comatose). More commonly, insidious onset of vestibular signs over the course of weeks to months is seen, which includes head tilt, ventral strabismus, and abnormal nystagmus (horizontal, rotary, or vertical). Associated cranial neuropathies, especially facial neuropathy, frequently occur ipsilateral to the lesion. Also, affected cats usually show profound obtundation and hemiparesis or tetraparesis. Patients with chronic disease often compensate, and vestibular signs may not be as marked as those occurring in acute cases. Clinical suspicion should be high for intracranial complications of otitis media/interna in cats that develop vestibular and/or brainstem signs in the face of recurrent ear infections.[3]

Pathophysiology

The pathogenesis of intracranial extension secondary to infection in the middle and/or inner ear may reflect the disease pattern. Intracranial infection extending from the middle and/or inner ear occurs either by direct extension (through progressive erosion of bone and soft tissues), hematogenously (with invasion of the endolymphatic system), or by following anatomically available pathways of vessels and nerves in the region.[4,5] Infection often occurs secondary to inflammatory polyps (see Chapter 38), but also may occur secondary to otic neoplasms or foreign body migration (e.g., plant awn, foxtail).[1,7] Clinical signs may be the result of extra-axial compression of the brainstem, secondary to abscess formation; infiltration and/or abscessation of the brainstem; or compression of nerve roots, secondary to inflammation and edema as they course through the petrous temporal bone and internal acoustic meatus (Figure 53-1).

Diagnosis

Clinical suspicion of bacterial meningoencephalitis secondary to otogenic intracranial infection should be on the differential diagnosis list of any cat with acute or chronic signs of vestibular/brainstem disease. In most situations, the animal has a history of chronic, recurrent ear infection; however, overt signs of otic disease may or may not be apparent at the time of development of neurological signs. A minimum database including bloodwork (complete blood count [CBC], serum

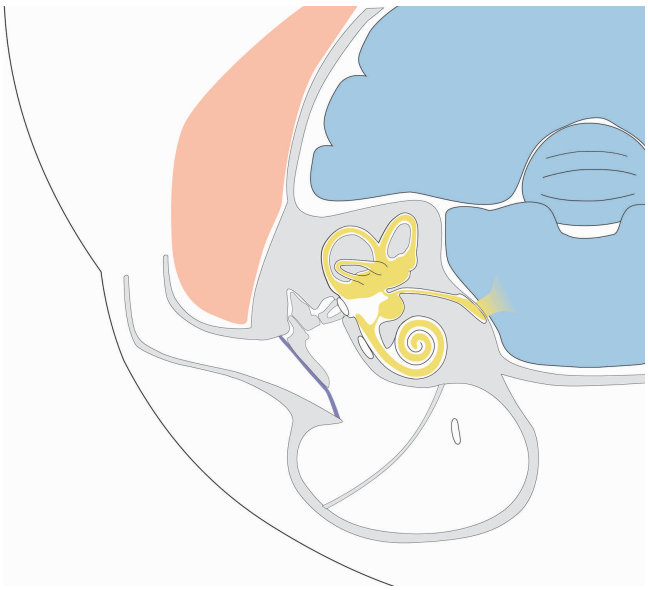
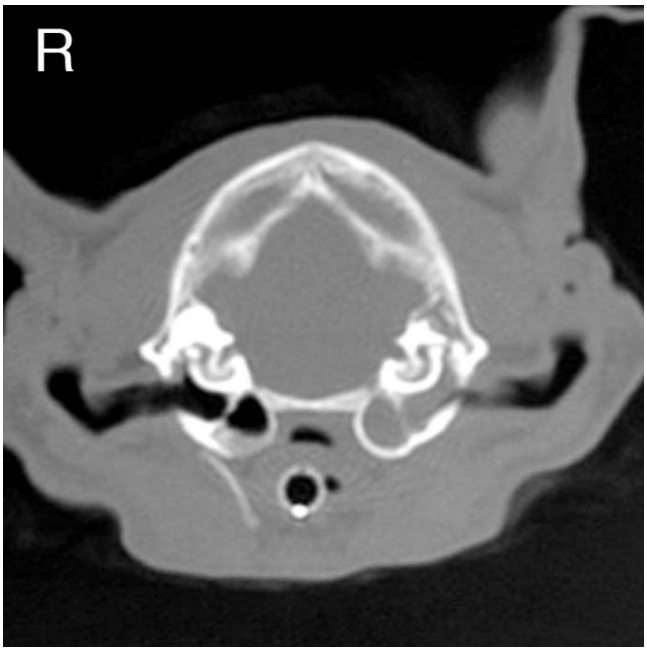


Figure 53-1. Regional anatomy of the middle and inner ear. The relationship of the intracranial nervous structures *(blue)* to the inner ear structures containing the vestibulocochlear system *(yellow)* can be seen. The vestibulocochlear nerve (cranial nerve VIII) enters the brainstem via the internal acoustic meatus. The two air-filled compartments *(white)* of the feline middle ear (bulla) are in connection with the external ear via the tympanic membrane (purple), and with the inner ear via the oval and round windows.

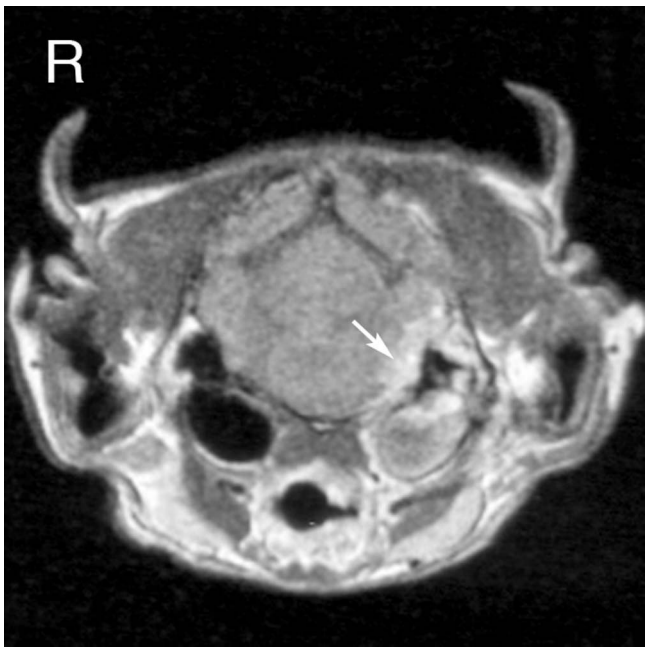
biochemistry profile, serum thyroxine [T_4], feline leukemia virus and feline immunodeficiency virus tests), urinalysis, thoracic radiographs, and abdominal ultrasound and/or radiographs, is performed to rule out extracranial diseases that may affect the brain. Abnormalities, aside from those caused by stress, are rarely present on the minimum database. After careful review of these diagnostic tests, advanced imaging is recommended. If access to advanced imaging is limited, skull radiographs may be obtained, looking for increased density in the region of the tympanic bulla on the affected side; however, diagnostic information relating to direct extension into the cranial vault usually is minimal.

Evaluation of the structures of the middle/inner ear and cranial vault using computed tomography (CT) and magnetic resonance imaging (MRI) has enhanced greatly the diagnosis of otitis media/interna with and without central complications.[9-12] CT is beneficial for delineating destructive bony lesions, but changes in extracranial soft tissues, brain parenchyma, and meninges may occur with little or no CT evidence, especially in the region of the brainstem in which beam-hardening artifact makes visualization of soft tissue structures difficult.[5,13] Contrast-enhanced MRI is the imaging modality of choice when otogenic intracranial infection is suspected. It is superior for visualization of changes in soft tissue and bony structures of the middle/inner ear in addition to brain parenchyma, and is essential for ruling out central extension of otitis media/interna definitively (Figure 53-2).[13]

Abnormal MRI features of cats with acute onset of vestibular/brainstem disease from extension of otitis media/interna include marked hyperintensity and apparent thickening of meninges and underlying neuropil on T2-weighted (T2W) MRI with contrast enhancement of the same structures on T1-weighted (T1W) images (Figure 53-3).[7,14] Imaging characteristics of subacute to chronic intracranial infection vary from plaquelike masses extending along the lateral and/or ventral aspect of the brainstem to globoid intraaxial or extraaxial masses causing marked brainstem compression. Mass lesions have variable intensity on T2W images and usually contrast enhance strongly on T1W images. Larger masses often have imaging characteristics typical of classical abscess formation (ring enhancement surrounding a more hypointense center on



A



B

Figure 53-2. Central extension of otitis media/interna. **A,** Post-contrast axial CT image at the level of the bullae. CT clearly demonstrates opacification of the left bulla suggestive of otitis media. **B,** Post-contrast axial T1W MRI. Central extension *(arrow)* was demonstrated in this case only after MR imaging.

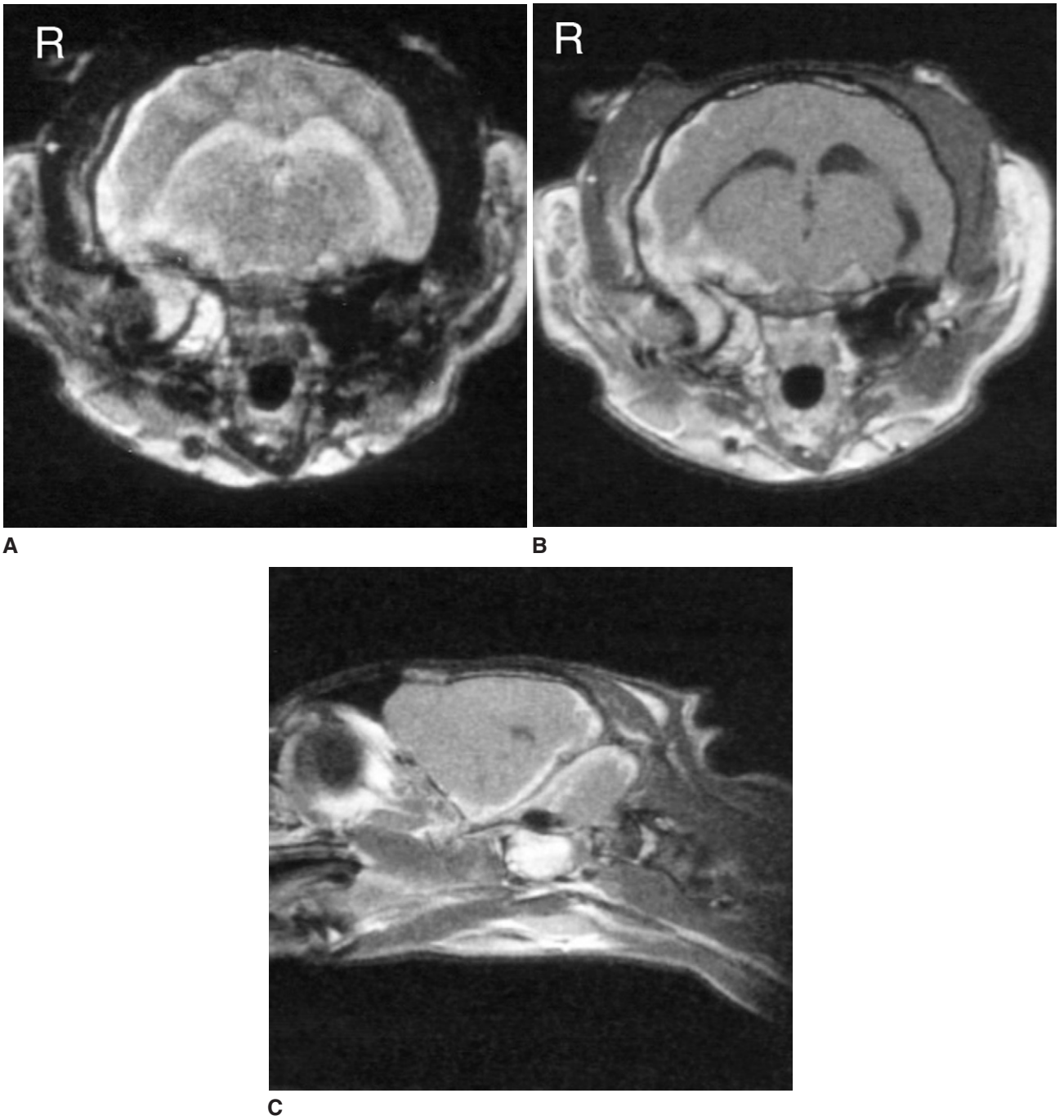


Figure 53-3. Acute central extension of otitis media/interna in a 1-year-old cat. **A,** Axial T2W MRI at the level of the bullae. **B,** Post-contrast axial T1W MRI. **C,** Post-contrast parasagittal T1W MRI. Diffuse meningeal involvement can be seen on both post-contrast T1W images and T2W images on the right side. Opacification within the right bulla also can be seen and delineates the ventromedial and dorsolateral compartments clearly. (Courtesy Sturges BK, Dickinson PJ, Kortz GD, et al. Otogenic intracranial infection in 10 cats and 4 dogs: clinical signs, magnetic resonance imaging features, and outcome after surgical and medical intervention, in press 2004.)

T1W images) and may expand rostrally from the brainstem to involve the midbrain and forebrain (Figure 53-4).[15] Nonuniform hyperintensity consistent with soft tissue and/or fluid densities within the affected bullae are seen on T2W with variable contrast enhancement on T1W images. Edema usually is present, although commonly mild and perilesional in nature. Occasionally marked, diffuse white matter edema is seen.

Evaluation of cerebrospinal fluid (CSF) is indicated except in situations with marked, rapid progression of neurological signs, which indicates severe intracranial hypertension and puts the patient at risk for cerebellar herniation, or in cases of obvious herniation of the cerebellum on MR imaging. Results of CSF analysis are extremely variable and range from normal to marked neutrophilic pleocytosis with or without intracellular bacteria (Figure 53-5). CSF culture is indicated when results

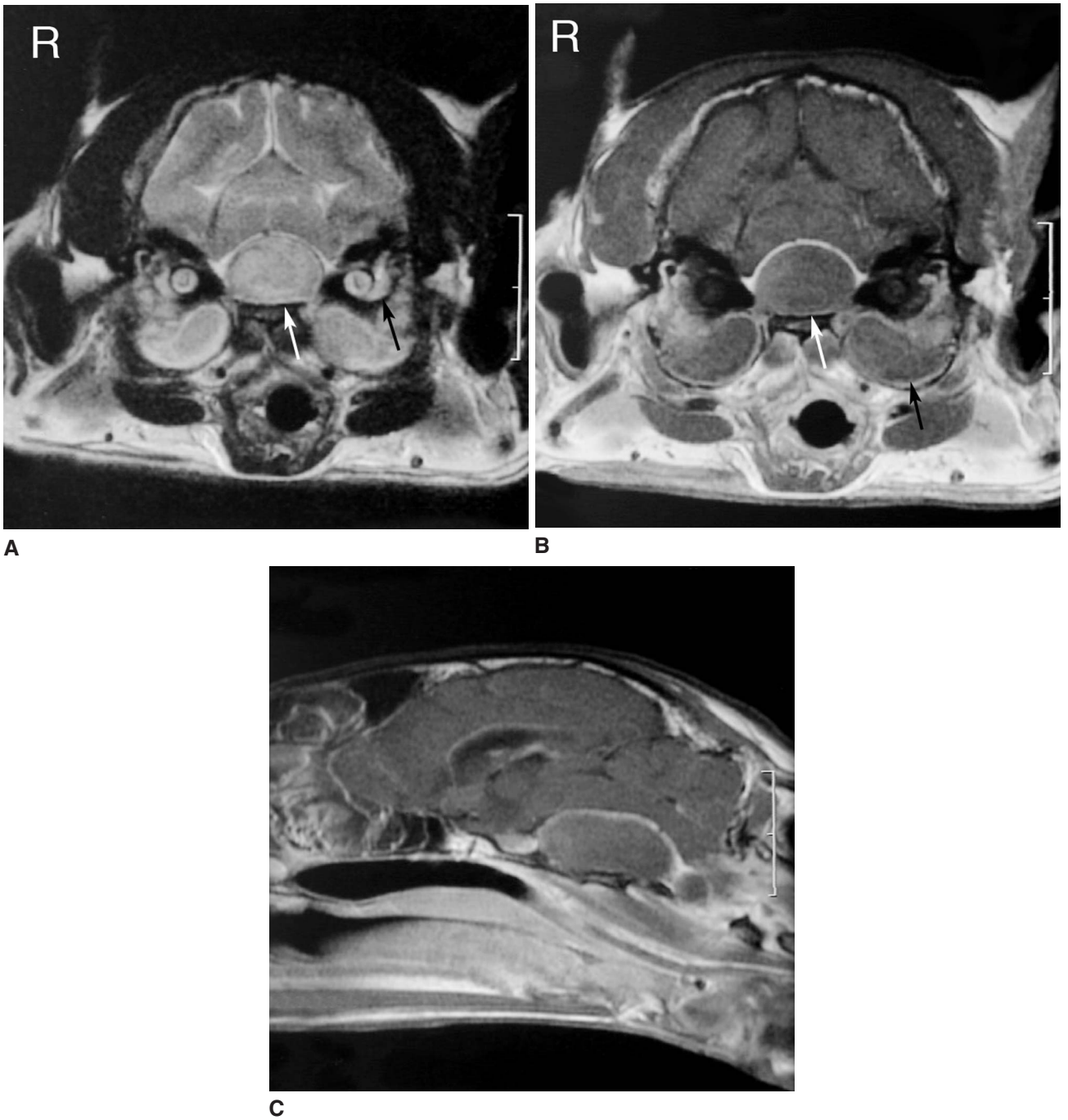


Figure 53-4. Central extension after chronic/recurrent ear infection in a 4-year-old cat with severe obtundation, ataxia, and central vestibular signs. **A,** Axial T2W MRI at the level of the bullae. **B**, Post-contrast axial T1W MRI. **C,** Post-contrast sagittal T1W MRI. A well-circumscribed abscess causing marked compression of neural structures can be seen ventral to the brainstem *(white arrows)*. The abscess can be seen extending from the level of the midbrain to beyond the foramen magnum on the sagittal image. Bilateral otitis media is present in this case. The cochlear structures within the inner ear can be seen clearly on T2W images *(black arrows)*.

are abnormal and clinical suspicion for intracranial infection is high.

Treatment and Outcome

Successful management of otogenic intracranial disease often requires aggressive therapy on an emergency basis. The objectives of the therapeutic regimen should be to eradicate the infecting organism, promote drainage by removing obstructive masses and necrotic tissue, and treat any underlying cause of otic disease.[5,6] Drainage is best accomplished surgically via ventral bulla osteotomy and curettage to remove all abnormal soft tissue and debris, followed by copious irrigation with saline. Any masses of soft tissue (e.g., inflammatory polyps, inflamed/infected soft tissues) extending into the cranial vault should be removed by gentle traction to establish drainage. Cultures are best collected from the surgical site and CSF because organisms cultured from the external ear canal may differ from

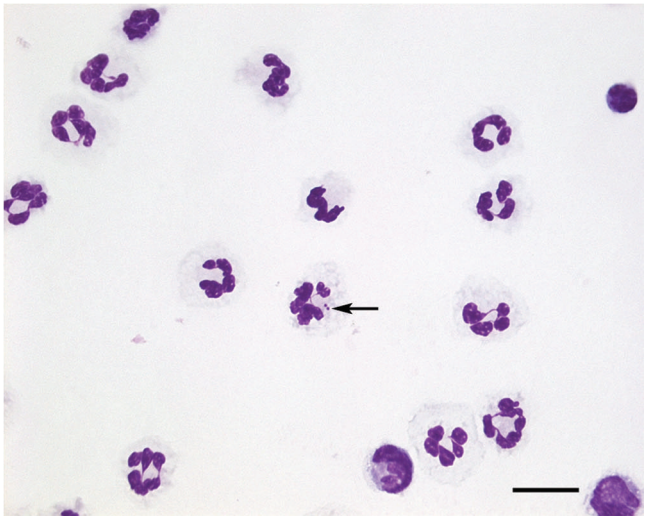


Figure 53-5. Otitis media/interna CSF cytospin preparation. Well-preserved, hypersegmented neutrophils with occasional intracellular cocci predominate *(arrow).* (Wright's stain. Size bar = 12 µm.)

those cultured from the bulla.[5,16,17] Bacterial cultures commonly yield *Staphylococcus*, *Streptococcus*, *Enterococcus,* and *Pasteurella* spp. Anaerobic organisms and gram-positive rods (e.g., *Actinomyces, Nocardia* spp.) are cultured occasionally, most frequently in association with foreign body migrations (e.g., foxtails or plant awns). Broad-spectrum intravenous antibiotics against aerobic and anaerobic bacteria should be started empirically pending culture results. Treatment with culture-specific antibiotics should be administered for a minimum of 1 to 3 months or until complete resolution of the lesions is seen on follow-up MRI and CSF has normalized (Figure 53-6).[6]

The effects of inflammatory mediators and cytokines are thought to be important causes of some of the neurological sequelae following bacterial meningoencephalitis secondary to otic infection.[5] Corticosteroids often are administered in human patients to lessen the inflammatory response and have not been found to alter antibiotic treatment.[18,19] Judicious use of anti-inflammatory doses of corticosteroids may be beneficial in cats that are severely affected neurologically.

Clinical response usually is dramatic over the course of 24 to 48 hours once appropriate and aggressive treatment has been initiated. Long-term prognosis is very good to excellent, although cats frequently are deaf on the affected side and may have residual vestibular deficits.

FELINE IMMUNODEFICIENCY VIRAL ENCEPHALOPATHY

Feline immunodeficiency virus (FIV) is a naturally occurring neurotropic lentivirus (retrovirus family) that causes immune suppression and neurological disease similar to that seen in HIV-infected people.[20] Neurological signs have been described in experimentally[20-27] and naturally[20,21,28-34] infected animals around the world. FIV infection of cats shares many clinical features with HIV infection of human beings, including a chronic course of disease, development of immunodeficiency, encephalopathy, and peripheral neuropathy. FIV-related neurological abnormalities have been reported in up to 33 per cent of ill FIV-infected cats.[21,33,35]

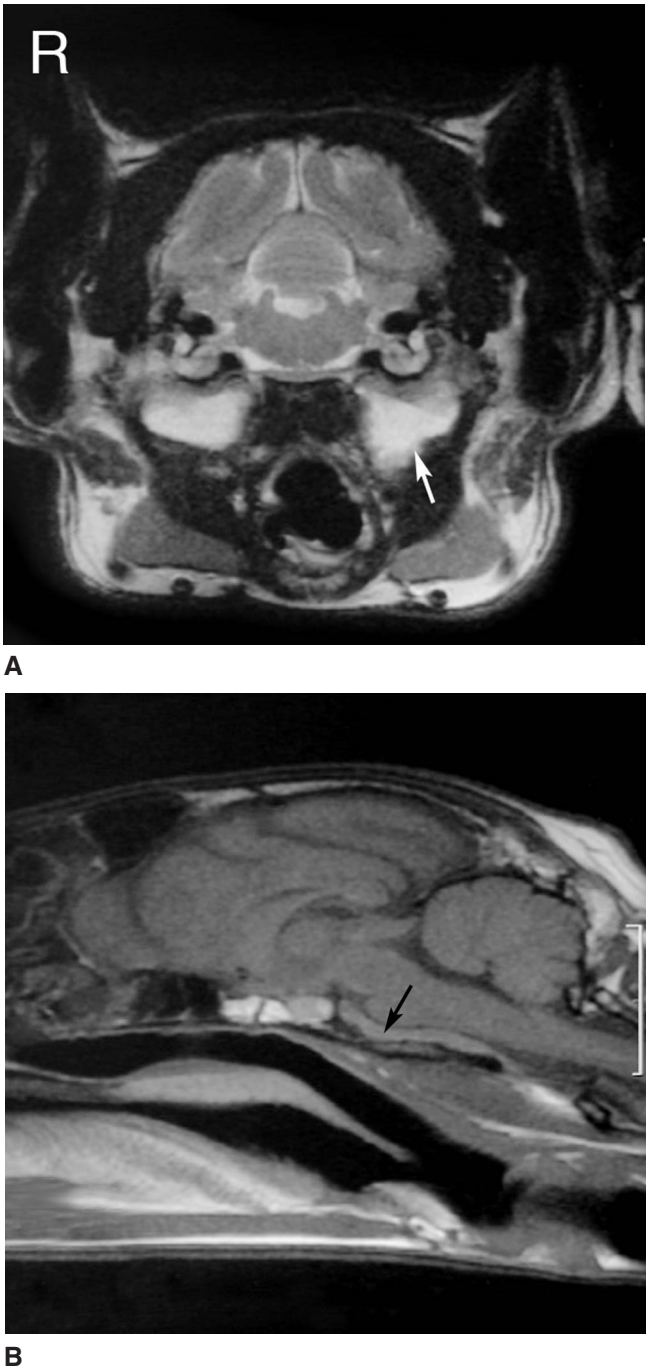


Figure 53-6. Six-week postoperative images of the same cat shown in Figure 53-5. **A,** Axial T2W image. **B,** Post-contrast sagittal T1W MRI. Drainage and resolution of the abscess can be seen on both images. Normal postoperative residual fluid and soft tissue density are seen within the bullae on T2W images *(white arrow).* Minimal soft tissue remains in the region of the abscess ventral to the brainstem *(black arrow),* which has returned to a normal anatomical position. The cat was neurologically normal 24 hours after surgery and appropriate antimicrobial therapy.

Pathogenesis

Biting is the predominant mode of transmission of FIV in cats. Although the virus is shed in the saliva, transmission by contact alone is uncommon as is transmission through the placenta or mammary glands.[21] Similar to HIV infection in people,

infection in cats occurs in essentially two stages. The initial stage of infection results in neutropenia, generalized lymphadenopathy, and fever leading to clinical signs of lethargy; sepsis may occur if the neutropenia is severe. This stage in most (naturally infected) cats goes unnoticed by the owner, and clinical recovery usually is complete. If persistent infection is established, cats become lifelong carriers of the virus. The AIDS-like stage of the disease usually occurs months to years later when cats present for opportunistic/secondary infections, myeloid or lymphoid tumors, and/or neurological signs. The age of the cat at the time of infection with FIV reportedly influences the onset and severity of FIV-associated encephalopathy. Kittens infected experimentally during the developmental period of brain maturation have more profound changes with an earlier onset of neurological dysfunction.[25,27]

Although FIV entry into the CNS is an early event in experimentally infected cats,[20,36] it is not known exactly when the virus enters the CNS in natural infection. However, it is becoming increasingly evident that a relationship between the presence of FIV in the brain and neurological signs is not straightforward. Most studies agree that FIV does not infect neurons, but exhibits trophism for microglial cells and astrocytes.[20] Virus reaches the CNS regardless of the route of infection, and intrathecal production of antibody usually can be detected within 6 to 8 weeks, with the brain likely remaining infected thereafter.[20] Histopathological findings include perivascular mononuclear cell infiltrates, glial nodules, and gliosis, predominantly in subcortical structures.[20,22,25,26,29] Multinucleated giant cells also have been described in a minority of cases.[22,29] Histopathological changes often exist even in cats with no overt neurological signs.[20-22]

Clinical Signs

Neurological disease usually occurs as a direct result of the virus itself rather than secondary to opportunistic infections such as *Toxoplasma* or *Cryptococcus* spp.; however, signs may occur alone or accompany other signs of systemic FIV infection. Encephalopathic signs, when detected, are typical of forebrain disease and may be subtle and nonspecific. Typical signs include ataxia, behavioral changes (hiding, aggression, inappropriate urination, compulsive roaming), reduced motor activity, and dementia.[21,27,29,35] Anterior uveitis has been reported in FIV-infected cats[23] (see Chapter 3), in addition to alterations in pupil diameter (anisocoria) and pupillary light reflexes, and excessive movements of the mouth and tongue.[25] Seizures and muscle twitching occur uncommonly.[21,23,35] Chronic, progressive encephalopathy and/or delayed onset dementias should raise the clinical suspicion of FIV-induced CNS disease.

Diagnosis

Cats that present with progressive encephalopathic signs should be evaluated carefully for metabolic, toxic, degenerative, neoplastic, and other infectious or inflammatory diseases of the brain such as feline infectious peritonitis, cryptococcosis, and toxoplasmosis. Extracranial causes of encephalopathy are ruled out with a comprehensive minimum database. Presumptive diagnosis of FIV infection as the cause of the clinical signs is made by positive serology for the virus and by excluding other intracranial causes of encephalopathy. Serum anti-FIV antibodies may be detected as early as 2 to 4 weeks post infection and usually remain at detectable concentrations for the lifetime of the cat.[21,37] Because a few experimentally infected cats have not shown detectable antibody for up to 1 year post infection,[37] retesting for antibodies may be useful if clinical suspicion for the disease remains high. Absence of antibody in FIV-infected cats, although uncommon, may reflect either early or late stages of the disease when animals have not yet seroconverted, or are so severely immunocompromised that serum antibodies are not present.[21,29,31] Antibodies may be detected using ELISA, IFA, or Western blot. Western immunoblot and IFA are not as sensitive as ELISA but have fewer false positive results (more specific) and should be performed to confirm a positive ELISA screening test. Alternatively, polymerase chain reaction (PCR) testing may be used to confirm the presence of proviral DNA.

Evaluation of CSF is important to rule out other potential causes of CNS encephalopathy, particularly other infectious/inflammatory disease and neoplasia. Nonspecific changes in the CSF, consistent with FIV infection, may precede the presence of antibodies by several weeks and include mild lymphocytosis and a normal or slight increase in protein content.[25,29,35] Intrathecal production of FIV antibodies detected in CSF that is free from blood contamination is strongly suggestive of CNS involvement and is seen in most infected animals. Virus also can be detected in CSF by special culturing techniques,[20,35] and proviral DNA may be detected with use of PCR.

Abnormal MR imaging of FIV-infected cats has not been reported. MRI is still recommended in the clinical assessment of cats with encephalopathic signs to rule out other differential diagnoses, even in the face of positive serology (blood or CSF) for FIV. Magnetic resonance spectroscopy (MRS) has been used in experimentally FIV-infected cats to detect and quantify the presence of neuronal injury[27] and may provide useful information in clinical cases. Changes in neurophysiological function, as assessed by delayed auditory and visual evoked responses in addition to electroencephalographic abnormalities, also have been reported with FIV-induced neurological disease.[25,36,38]

Treatment

No effective treatment to ameliorate neurological signs associated with FIV infection has been reported in the clinical setting. Immune modulators such as acemannan and *Propionibacterium acnes* have been proposed as possible treatments; however, controlled data are scant and results have been disappointing. Inhibitors of retroviral reverse transcriptase such as azidothymidine (AZT) and phosphonomethoxyethyladenine (PEMA) have been shown to have efficacy in the treatment of experimental and naturally occurring FIV infections. Improvements in stomatitis and overall clinical condition have been seen, although no evidence of efficacy in infected cats with neurological signs is available.[39,40] Significant complications may occur including anemia and development of resistance because of enhanced mutation of the virus. The newer class of antiviral drugs, the protease inhibitors, generally have yielded disappointing results in FIV-infected cats; however, a recently developed broad-based inhibitor, TL-3, has been shown to counteract the effects of FIV on the CNS of experimentally infected cats.[41] Symptomatic therapy such as the use of anticonvulsant medications, or the treatment of secondary complications of FIV infection, is the mainstay of treatment at this time.

Prevention

The most effective means of preventing FIV infection is to prevent exposure. Testing of newly adopted or sick cats is recommended, particularly in multiple-cat households, and FIV-positive cats should be segregated from FIV-negative cats. Although an encouraging commercial FIV vaccine (Fel-O-Vax FIV, Fort Dodge Animal Health, Overland Park, KS) is available, its efficacy against a variety of FIV genetic variants in the field has not been proven. Vaccination results in false-positive test results with the currently available serological assays,[42] making recommendation to vaccinate difficult for cats not at high risk. Future availability of tightly controlled, highly specific real time PCR diagnostic tests for proviral DNA may differentiate vaccinated from naturally infected animals and help to resolve some of these problems.

HIPPOCAMPAL NECROSIS

The limbic system is an area of the brain composed of several anatomical components, including the hippocampus and piriform lobe, and is associated with basic functions such as emotion and behavior. A profound encephalopathy of cats, caused by necrosis of the hippocampus, has been described infrequently in the veterinary literature.[43,44] The syndrome is characterized by progressive, partial and generalized seizure activity, behavior changes (particularly aggression), and pathological features confined to the limbic system. Reported cats in the literature did not respond to classical seizure therapies, and died or were euthanized because of severe neurological signs.

In recent years, the authors have seen six cats fitting the reported clinical syndrome of hippocampal necrosis. The cats were otherwise healthy with normal extracranial and intracranial diagnostic evaluations, including MR imaging and CSF analysis. Three of the cats survived after a prolonged and difficult recovery with medically manageable seizure disorders. One of these cats died from an apparently unrelated cause 1 year later and was confirmed to have hippocampal necrosis. The other three cats died within days after presentation in spite of intensive therapy for the seizures. All cats necropsied (four of six) had bilateral hippocampal necrosis. One of the surviving two cats showed abnormalities in the limbic system on MRI.

Additionally, hippocampal necrosis has been seen at the authors' institution in 12 other cats with acute onset of encephalopathic signs when the animals were affected with other systemic diseases. Although an acute onset of poorly controllable seizures and mentation changes were present consistently, these cats were less likely to exhibit aggressive behaviors. Necropsies confirmed the diagnosis of hippocampal necrosis and an underlying organic disease process, usually of a chronic, progressive nature including hepatic lipidosis, pulmonary diseases, and renal diseases. In many cats, clinical signs frequently occurred hours to days after apparent recovery from short anesthetic procedures.

Epidemiology and Etiology

To date, published reports on cats with hippocampal necrosis have been restricted to Europe; however, the disease appears to occur in North America. No consistent findings relate to signalment, history, or potential risk factors. Although no known etiological agent exists, the acute clinical signs and bilateral, symmetrical nature of the pathology strongly suggest an ischemic, metabolic, or toxic insult to the brain.

Clinical Findings

Cats present characteristically with an acute onset of partial or generalized seizures that progress rapidly in frequency and severity over a few days. Aggression, rage (uncontrolled biting), facial twitches, and salivation are seen commonly. Cats may have altered consciousness, may be unpredictable in their response to sensory stimuli, and often are very difficult to handle. Between episodes, fear, aggression, restlessness, and hyperexcitability predominate. Even with treatment, many cats progress to blindness, stupor/coma, and/or status epilepticus.

Diagnosis

No definitive antemortem diagnosis exists for hippocampal necrosis. The acute onset of profound, progressive neurological signs including seizures and marked behavioral changes in an otherwise healthy cat (or in a cat with a chronic progressive disease that begins unexpectedly to exhibit seizures) should raise the index of clinical suspicion. Seizures and episodes of abnormal behavior characterized by fear, aggression, and hyperexcitability are strongly suggestive of disease affecting the limbic system of the brain. Extracranial diagnostic tests, including CBC, serum biochemistries, urinalysis, serology for FIV/FeLV, thoracic radiographs, and abdominal ultrasound usually are within normal limits. In cats in which hippocampal necrosis is associated with or occurring secondarily to systemic disease, no specific alterations in the diagnostic tests for that condition have been found.

CSF analysis usually is normal.[43,44] In our experience, although the total nucleated cell count usually is within normal limits, the relative distribution of cells is abnormal with higher than normal percentages of neutrophils (varying from 10 to 80 per cent), consistent with prolonged seizure activity. In a few cats, transient mixed pleocytoses have been observed that normalize within a few days of obtaining control of the seizures. No published reports exist on the MRI findings of cats with hippocampal necrosis. MR imaging performed on four cats seen in our clinic with confirmed hippocampal necrosis has been within normal limits. One cat in which a tentative diagnosis of hippocampal necrosis was made had MRI findings consistent with lesions within the hippocampus. Presence or absence of MRI abnormalities may depend on the time of imaging relative to the onset and progression of the condition (Figure 53-7).

Pathology

No gross lesions are observed generally in the CNS of cats with hippocampal necrosis. Light microscopic lesions include bilateral, degenerative necrosis in the hippocampus and/or the piriform lobe. The type of neuronal damage is classified morphologically as ischemic necrosis that occurs typically in association with excitotoxicity and ischemia. In human beings, the hippocampal formation is particularly vulnerable to excitotoxic damage resulting from seizures and ischemia.[45] In veterinary clinical medicine, ischemic lesions, especially those that involve the hippocampus, usually have been considered a result rather than the cause of seizures.[46] However, the fact that the

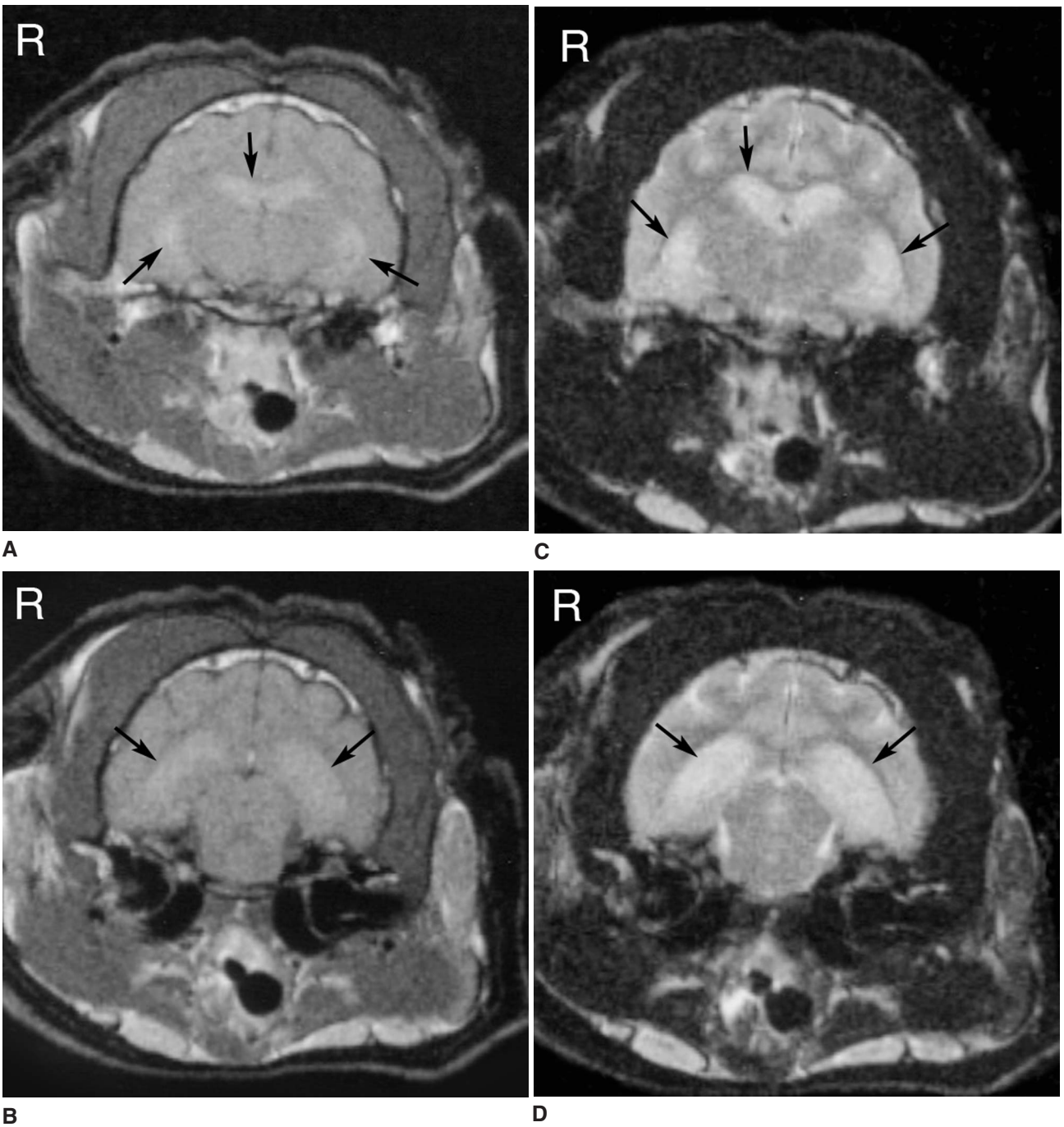


Figure 53-7. Suspected hippocampal necrosis. **A** and **C,** Post-contrast axial T1W, T2W MRI at the level of the thalamus. **B** and **D,** Post-contrast axial T1W, T2W MRI at the level of the midbrain. Contrast enhancement (T1W) and hyperintensity (T2W) can be seen outlining the hippocampus *(arrows).*

majority of cats euthanized because of severe seizure disorders do not have these pathological findings, together with the specific clinical syndrome seen with hippocampal necrosis, suggests that underlying idiopathic epilepsy is unlikely to be the cause of the condition. However, once the cycle is established, uncontrolled or severe seizures may propagate neuronal destruction of the ischemic type. It is unclear whether cats already compromised from pre-existing systemic disease may be more susceptible to whatever the underlying cause of hippocampal necrosis is, or whether the presence of systemic disease is coincidental.

Treatment and Prognosis

Aggressive antiepileptic drug therapy includes standard treatment protocols for status epilepticus commenced as soon as possible to achieve satisfactory seizure control (see Chapter 55). The use of constant rate infusions of benzodiazepines (valium, midazolam), barbiturates (phenobarbital, pentobarbital), and/or general anesthetics (e.g., isoflurane) may be required to abolish clinical seizure activity. Intensive supportive care usually is necessary to treat the seizures in addition to complications arising from the seizures. Continuous (or

frequent intermittent) monitoring of body temperature, heart rate, and blood pressure is done until seizures are controlled and the cat is stable. Monitoring of serum electrolytes, blood glucose, blood lactate, and blood gases is performed to detect and treat potential complications of prolonged seizures such as aspiration pneumonia, hypoglycemia, and electrolytic imbalances. Cats are maintained on appropriate fluid therapy until seizures are controlled to ensure euvolemia and to prevent renal damage from release of myoglobin as a result of prolonged seizure activity. Cats whose seizures are controlled may have abnormal behaviors for weeks to months. Specific counsel should be given to the owners of such cats especially if small children are in the household. Cats that survive should remain on anticonvulsant drugs indefinitely.

PHAEOHYPHOMYCOSIS

Etiology and Epidemiology

Phaeohyphomycosis is the term given to invasive disease caused by several species of dematiaceous fungi, pigmented molds containing melanin in their cell walls. The characteristic dark-walled mycelia and/or yeast-like cells are present in cultures of the fungus and on microscopic examination of infected tissues. In spite of variation in individual morphological criteria that identify the various species of melanoid fungi, the illnesses they produce have many common features[47-49] (see Chapter 7).

Dematiaceous fungi are widespread in the environment, primarily as soil saprophytes but also as plant pathogens.[50] These potentially pathogenic fungi also have been isolated from the skin and hair coat of healthy cats and cats infected with FIV or FeLV.[51,52] Most of the species are considered opportunistic, although a few may be true pathogens.[53] The agents of phaeohyphomycosis are found worldwide, although the reported cases of feline CNS involvement have been from North America, Australia, and Europe.[54-62]

Infection occurs in cats, dogs, human beings, and many other vertebrate species. Cats may be more susceptible than other animals to these fungi because more reported cases are described in cats than in other animal species. The spectrum of feline phaeohyphomycoses ranges from cutaneous/subcutaneous infection (see Figure 7-1) to rapidly progressive, systemic disease. Cerebral disease is the most common form of systemic infection, with other organs affected much less frequently. Of 51 reported cases of feline phaeohyphomycosis, 11 were intracranial,[54-62] and only one of these had other organ involvement.[56] Most of the remaining reported cases of phaeohyphomycosis have been infections of the skin and subcutis.

Several species of dematiaceous fungi have been reported to cause CNS phaeohyphomycosis; however, *Cladophialophora bantiana* (known previously as *Torula bantiana*, *Cladosporium bantianum*, *Cladosporium trichoides*, and *Xylohypha emmonsii*) is the species isolated most frequently in cats and human beings,[63,64] and is considered to be one of the most pathogenic fungi known to date.[65] One of the factors that may be responsible for its virulence is the presence of melanin that actually may provide protection against host defenses.[53] Although this species can cause subcutaneous and other systemic infection, it is considered to be neurotropic,[64,65] possibly associated with the acquisition of a 558bp ribosomal DNA intron sequence.[65] Other dematiaceous fungi cultured from cats with CNS disease include *Ochroconis gallipavum*,[59] *Phoma eupyrena*,[57] and *Exophiala jeanselmei*.[56]

Pathogenesis

The pathogenesis of primary CNS phaeohyphomycosis remains unknown. Inhalation of molds with subsequent hematogenous spread or contiguous spread from local infection is considered the most likely mode of infection.[64,66] Cutaneous and subcutaneous infections with dematiaceous fungi in cats are thought to occur primarily through traumatic inoculation. None of the reported cats with CNS disease had signs of sinusitis or otitis media/interna to suggest local extension of an infectious focus, and only two ocular-related cases had a history consistent with local extension.[58,67] The histopathological distribution of brain lesions in most cases, however, is typical of embolic spread with fungal elements present frequently in vessel walls, and CNS infection has been induced experimentally in one cat with intravenous injection.[68] Hematogenous spread probably is the source of CNS infection in most feline cases. A cutaneous route of cerebral infection may occur as has been reported in one dog with CNS phaeohyphomycosis.[69]

Immune deficiency has long been considered a risk factor for mycotic infection in animals and human beings. However, only one of the reported feline cases was possibly associated with immune compromise.[60] Likewise, the other forms of phaeohyphomycosis in cats (e.g., cutaneous and subcutaneous disease) are associated uncommonly with immune deficiency.

Clinical Signs

The clinical signs of cerebral phaeohyphomycosis reflect the anatomical location of the lesion(s) and often are severe and rapidly progressive. Multifocal or diffuse CNS signs (obtundation, ataxia, paresis, seizures, pupillary changes, vestibular signs) were reported in most of the cats, although the lesions, diagnosed as discrete abscesses, were restricted to the frontal lobes of the brain in 7 out of 11 cases. The severity of neurological signs at the time of presentation along with the rapid deterioration in neurological status suggests that brainstem signs often are secondary to marked elevation in intracranial pressure.

Diagnosis

No reported cases of feline cerebral phaeohyphomycosis have been diagnosed antemortem. After a comprehensive minimum database to define related and unrelated concurrent systemic disease, MRI and CSF evaluation are indicated to rule out other causes of encephalopathy and to define the anatomical location of any lesion(s). Serology for FeLV and FIV is performed to rule out potential causes of immunosuppression. Definitive diagnosis likely requires stereotactic or open surgical biopsy of lesions as reported previously in human beings and dogs.[70-72] Histopathology must be done together with mycology to diagnose infection by dematiaceous fungi definitively, and to rule out the possibility that cultures are laboratory contaminants (Figure 53-8). Culture and isolation of fungal elements from tissue is necessary for species identification in addition to in vitro sensitivity testing. Occasionally the organisms are not pigmented in infected tissues, and melanin stains, such as Fontana-Masson, may be needed to identify pigment in fungal

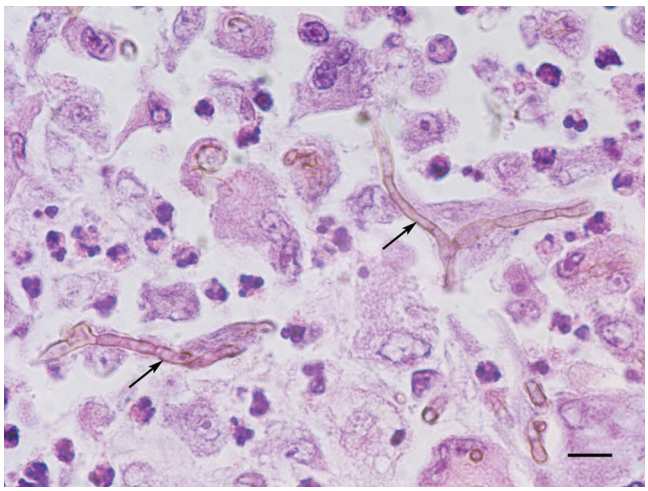


Figure 53-8. Cerebral phaeohyphomycosis. Characteristic brown pigmented fungal elements *(arrows)* can be seen within a CNS abscess. (Hematoxylin and eosin. Size bar = 12 μm.)

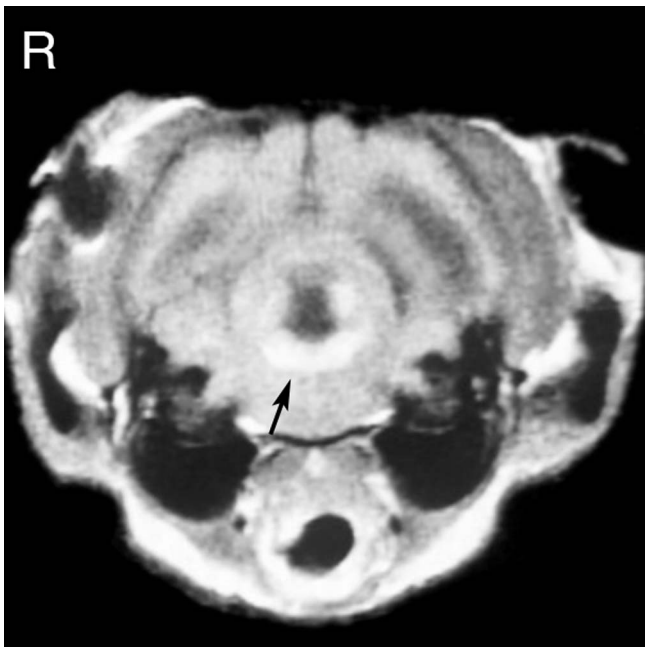


Figure 53-9. CNS phaeohyphomycosis (*Phoma eupyrena*). Post-contrast axial T1W MRI at the level of the fourth ventricle. Ventriculomegaly can be seen affecting the fourth and lateral ventricles. Periventricular contrast enhancement also is present *(arrow)*. Similar MR findings may be seen with FIP and lymphoma, which should be primary differential diagnoses in such cases.

cell walls. In early stages of infection, hyphal elements often are hyaline rather than melanized, and because many laboratories do not apply melanin-specific stains routinely, cases of phaeohyphomycoses may be diagnosed incorrectly as cerebral aspergillosis.[48]

MRI and CT reports of cerebral phaeohyphomycosis in human beings usually describe a ring-enhancing lesion with associated edema and mass effect.[72,73] No reports exist of MRI findings in cats with phaeohyphomycosis, although an MRI was performed on the cat diagnosed with brainstem *Phoma eupyrena* consistent with ependymitis and ventriculomegaly (Figure 53-9). CSF analysis, consistent with pyogranulomatous inflammation with no evidence of fungal elements, was reported in four cats from which CSF was collected.

Treatment

Treatment of feline cerebral phaeohyphomycosis to date has been unsuccessful in cases treated symptomatically, or not attempted because of rapid neurological deterioration of the patient. Long-term survival of human patients has been reported with complete surgical resection of discrete lesions.[53,64] Antifungal treatment may be of benefit when surgical resection is incomplete or when the location of the infection in the brain renders surgery unfeasible.[53,64,74] Activity of all reported antifungal drugs against infections with dematiaceous fungi is unpredictable. The combination of amphotericin B, 5-fluorouracil, and itraconazole in treatment of CNS phaeohyphomycosis has been associated with improved survival in human beings.[53] Clinical use of the newer azoles (e.g., voriconazole, posaconazole, ravuconazole) has yet to be evaluated. Among the antifungal agents available, both itraconazole and voriconazole have consistent, potent antifungal activity with oral and intravenous formulations available. Voriconazole has shown good broad-spectrum activity in vitro against most pathogenic yeasts, dimorphic fungi, and opportunistic molds.[75,76] Both drugs achieve good penetration into brain tissue and both have been used successfully to treat non-CNS phaeohyphomycosis.[77-79] Posaconazole and ravuconazole are newer azole derivatives that have potent, broad-spectrum antifungal activity in vitro against dematiaceous fungi. Preclinical studies of posaconazole in mice show that it may be broadly effective against CNS phaeohyphomycosis.[80] 5-Fluorouracil has excellent CSF penetration in mice and has shown activity against dematiaceous fungi, particularly *Cl. bantiana*.[81] Although amphotericin B has long been the gold standard for therapy of fungal infections, adverse effects, particularly nephrotoxicity, and resistance, can be problematic. The use of lipid preparations of amphotericin may have better penetration into brain parenchyma and allow use at higher doses with longer treatment regimens.[53]

Outcome

Based on the available data, prognosis for survival in cats with CNS phaeohyphomycosis is grave. Overall mortality rates in human beings are reported as 73 per cent and are similar for immunocompetent and immunocompromised patients. Increased availability of stereotactic biopsy procedures and antemortem diagnosis may improve management of feline cases in the future.

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Chapter 54

BRAIN TUMORS

Karen M. Vernau and Peter J. Dickinson

INCIDENCE

Several studies report the frequency,[1] incidence,[2,3] and relative risk[4] of intracranial neoplasia in domestic animals. Population-based animal studies are very difficult to execute,[4] and thus most studies are based on information provided by groups of veterinary hospitals or groups of veterinary teaching hospitals; therefore they must be interpreted with caution. Information from these studies about feline intracranial neoplasia is limited.

The incidence and prevalence of spontaneous intracranial neoplasia in cats are not known. Two commonly cited studies report crude incidence rates, based on necropsy surveys from referral hospitals.[5,6] Because the results of necropsy surveys are not generalizable to the population of an area,[7] the prevalence and incidence of feline intracranial neoplasia remain unknown.

Despite the lack of prevalence or incidence data, it is commonly accepted that feline intracranial neoplasia is rare and less common than in dogs.[8-11] Several studies describe central nervous system (CNS) tumors in cats but do not separate brain tumors from spinal cord tumors.[12,13]

Meningiomas are the most common intracranial neoplasm in cats and have been reviewed extensively elsewhere.[14] Intracranial neoplasms other than meningiomas do occur and are the second most common brain tumor.[9,15] Most reports of brain tumors other than meningiomas in cats are case reports, case series, embedded in book chapters or necropsy surveys, which limits the ability to make definitive statements for many tumor types.

In a large, recent, retrospective study in which the majority of the tumors were meningiomas, 16 cats (10 per cent) had two or more discrete intracranial tumors of the same type. Another 16 cats (10 per cent) had two different types of intracranial neoplasms. The tumor was incidental in 30 cats (18.8 per cent). Four cats (2.5 per cent) had another type of neoplasm outside the nervous system. The location of tumors was mostly supratentorial (158 tumors, 87.3 per cent), infratentorial (six tumors, 3.3 per cent), and both supratentorial and infratentorial (17 tumors, 9.9 per cent).[16] This chapter discusses intracranial neoplasia, other than meningiomas, in cats (reviewed previously in *Consultations in Feline Internal Medicine*, volume 4, Chapter 50).

DIAGNOSIS

Localization of intracranial disease and formulation of an appropriate list of possible causes are based initially on history, signalment, and physical and neurological examinations.

Neoplasia generally is more likely in older animals with a progressive history of neurological signs, or in specific medical conditions that are suggestive of intracranial neoplasia (e.g., pituitary dependent hyperadrenocorticism or acromegaly). A thorough minimum database is essential in all animals suspected of having intracranial neoplasia to define the presence of multifocal or locally invasive neoplastic disease and concurrent systemic disease that may affect prognosis and planned diagnostic procedures. A minimum database for a cat with brain disease should include a complete blood count, serum biochemistry analysis, urinalysis, thoracic radiographs, abdominal ultrasound, and blood pressure measurement.

Although radiography may be informative in cases of secondary tumors invading the cranial vault, advanced imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are the preferred diagnostic procedures for delineation of intracranial neoplasia. Cerebrospinal fluid (CSF) analysis often is abnormal but frequently nondiagnostic. Specific diagnosis based on the actual presence of neoplastic cells is more common with tumors such as lymphoma, although CSF neoplasia also has been noted with oligodendroglial and plasma cell neoplasia. The decision to collect CSF ideally should be made based on clinical signs and advanced imaging, in order to minimize morbidity and mortality associated with brain herniation in cats with clinical or imaging characteristics suggestive of raised intracranial pressure (e.g., cerebellar herniation).

The CT and MRI characteristics of tumor types are published[17-20] and imaging characteristics of tumors are described below for each tumor type; however, imaging often does not provide a specific diagnosis.[21] Tumor location, together with imaging characteristics, may help to define the most likely differential diagnoses (Table 54-1); however, definitive diagnosis is based on the results of biopsy, cytology, and histopathology. Open surgical or stereotactic CT–guided biopsy[22] of tumors ideally should be performed, to obtain an accurate antemortem

Table 54-1 | **Typical Reported Characteristics of More Common Feline Intracranial Neoplasia**

HISTOLOGICAL TUMOR TYPE	PREDILECTION SITE	PATHOLOGY	MRI EDEMA	MRI CONTRAST ENHANCEMENT
Astrocytoma	Rostrotentorial intra axial	Solitary	Variable	Heterogeneous (+/– ring)
Oligodendroglioma	Rostrotentorial intra axial (+/– ventricular)	Solitary	Variable	Heterogeneous (+/– ring)
Ependymoma	Rostrotentorial ventricular (3rd ventricle)	Solitary, 2° hydrocephalus	Unknown	Uniform
Olfactory neuroblastoma	Nasal cavity, olfactory, bulb/frontal lobe	Solitary; erosion of cribriform plate	Moderate to severe	Heterogeneous
Lymphoma	None	Solitary or multifocal	Moderate to severe	Usually homogeneous
Pituitary tumors	Diencephalon	Solitary	Minimal	Usually homogeneous

diagnosis and thus allow for a more appropriate and informed approach to therapeutic planning.

TREATMENT

Information relating to conventional treatment modalities for feline brain tumors, other than meningiomas, is limited and anecdotal. Surgical resection/debulking, radiotherapy, and chemotherapy are the most common treatments reported, in addition to the palliative use of anti inflammatory doses of corticosteroids to reduce peritumoral edema, and anticonvulsant medications to treat symptomatic epilepsy. Chemotherapy has been limited essentially to treatment of lymphoma, using standard protocols, and the anecdotal use of nitrosourea alkylating agents such as lomustine (CCNU) for primary brain tumors. Protocols for lomustine therapy in cats have been published; however, information relating to its efficacy in the treatment of brain tumors has not. Because of the limited information available, specific references regarding treatment and prognosis, where available, are discussed individually for each tumor type.

CLASSIFICATION

Intracranial neoplasia is classified as primary or secondary. Primary intracranial neoplasia is defined as a tumor that originates from cells that normally exist within the brain or meninges (neuroectoderm or mesoderm).[23] Secondary intracranial neoplasia is a tumor that originates from cells that normally exist outside of the brain or meninges that metastasize to the brain or affect the brain by compression or local invasion.[23]

Primary Intracranial Neoplasia

The frequency of primary intracranial neoplasia was more common (70.6 per cent) than secondary intracranial neoplasia (29.4 per cent) in one study.[16] Meningiomas were the most common type of primary intracranial neoplasia, with a frequency of 58.1 per cent.[16] Neoplasms are classified according to their cell of origin based on the World Heath Organization classification system.[24]

Cells of Neuroepithelial Origin

ASTROCYTOMA. An astrocytoma is a glioma composed of neoplastic astrocytic cells. After meningiomas, astrocytomas are the second most common primary intracranial neoplasm in cats. Astrocytomas in one study had a frequency of 2.8 per cent of all feline brain tumors[16] and in another study were "moderately common."[15] To our knowledge, 34 cats are reported with astrocytomas; most reports are necropsy surveys or case reports.* Cats ranged from 1 to 16 years of age. The 1-year-old cat had a concurrent feline infectious peritonitis infection.[30]

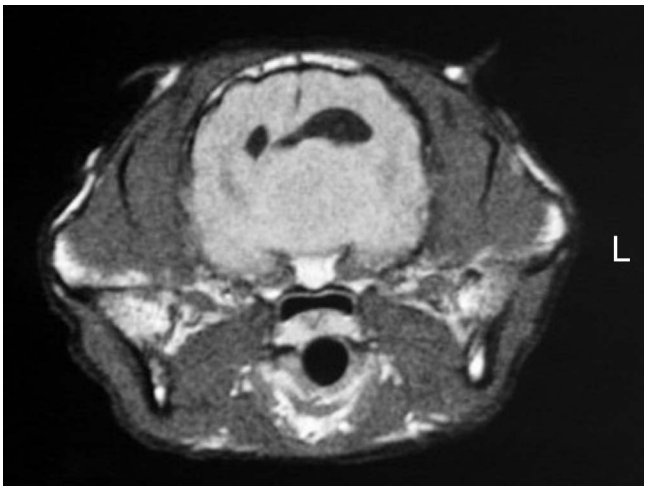
Most astrocytomas are supratentorial and involve the cerebrum predominantly with occasional involvement of the lateral ventricles.[16,32] The tumors involved the brainstem,[30,31] and three were multifocal (brain and cervical spinal cord).[30] The WHO grades astrocytomas into four groups, I (pilocytic), II, III (anaplastic), and IV (glioblastoma) based on characteristics of increasing malignancy. Several subtypes are reported in cats including three glioblastoma multiforme,[16,28,29] one "malignant" astrocytoma,[31] one subependymal giant cell tumor,[32] one pilocytic,[30] two fibrillary,[8,30] two protoplasmic (one was multifocal),[30] and three gemistocytic (one was multifocal).[16,30] One multifocal astrocytoma had fibrillary, protoplasmic, and gemistocytic components.[30]

Common clinical signs included seizures (three cats had seizure episodes for 1 to 3 years),[28] behavior change, altered consciousness, and upper motor neuron tetraparesis. Two cats had central vestibular signs.[30,32]

Two brief descriptions of the CT imaging characteristics of a feline intracranial astrocytoma have been reported.[19,35] In one report, a thalamic mass was described as uniformly contrast-enhancing.[35] In the other report, a rostral cerebral mass was not apparent on non-contrast images but was moderately ring-enhancing post contrast.[19] The MR features of astrocytomas and oligodendrogliomas were grouped together in one report (one astrocytoma and three oligodendrogliomas), and thus the specific appearance of feline intracranial astrocytomas is unknown. All four gliomas were intraaxial; two had mass effect. Tumors were hypointense on T1-weighted (T1W) images with ring enhancement and had variable contrast enhancement. They were hyperintense on T2-weighted (T2W) images, with mild to moderate peritumoral edema. Three of the four tumors had cystic components (Figure 54-1).

In three cats, astrocytoma was diagnosed using wet-fixed smears of brain tissue collected by a CT-guided stereotactic brain biopsy.[22] Cytologic characteristics of astrocytomas

*References 7,9,11,16,19,25-34.



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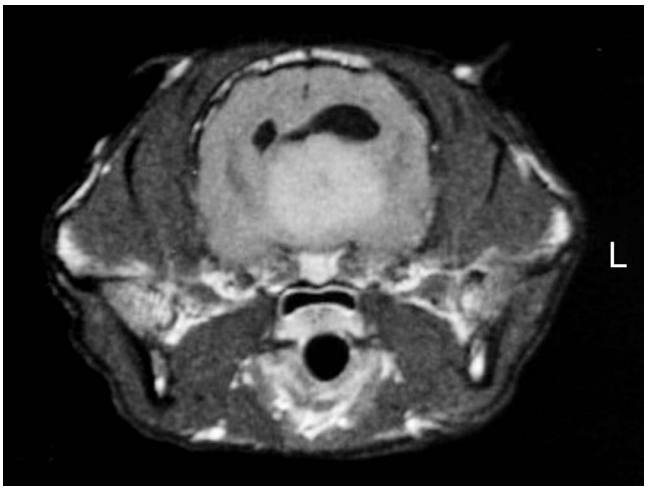

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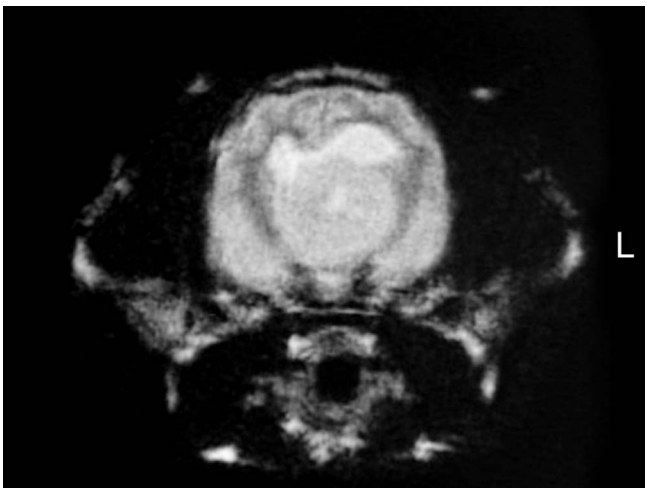

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Figure 54-1. Astrocytoma. Transverse MRI at the level of the temporomandibular joint from a 9-year-old MC DSH cat. **A,** T1W image. **B,** T1W post-contrast image. **C,** T2W image. An intraaxial, moderately contrast-enhancing thalamic mass, with moderate mass effect is noted.

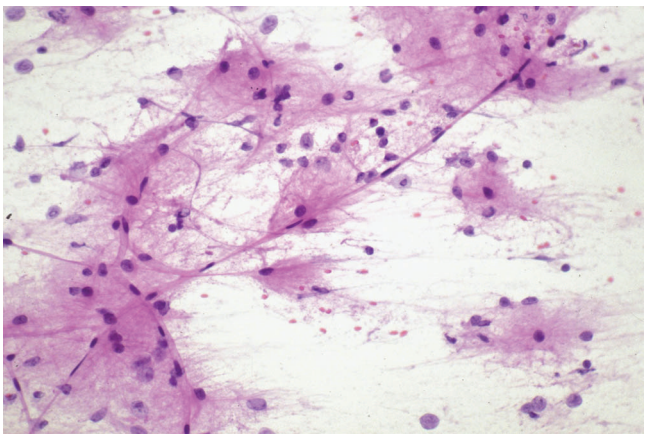


Figure 54-2. Astrocytoma. Wet-fixed smears of brain tissue collected by a CT-guided stereotactic brain biopsy. Hematoxylin and eosin stain. Note the presence of thin walled, well-defined branching blood vessels. Tumor cells have elongate nuclei, minimal cytoplasm, and an extensive network of fibrillary cytoplasmic processes.

include moderate hypercellularity compared with normal brain and presence of thin-walled, well-defined branching blood vessels. Tumor cells had elongate nuclei, minimal cytoplasm, and an extensive network of fibrillary cytoplasmic processes (Figure 54-2).[34]

Two cats were diagnosed after craniotomy and debulking surgery; however, most diagnoses were reached after euthanasia and necropsy at presentation. Almost no data are available regarding response to treatment; one cat died 1 day after surgery; the other cat had two surgeries and megavoltage irradiation post surgery and lived for 179 days.[16]

OLIGODENDROGLIOMA. Oligodendrogliomas are a glioma composed of neoplastic oligodendroglial cells. They are reported sporadically in cats and involve only the brain. We are aware of nine reports in the veterinary literature with 14 individual cats,[8,16,17,36-41] although one cat was described as an oligoastrocytoma.[8] No obvious breed or sex predilection exists, with tumors reported in domestic short-haired (DSH) cats and domestic long-haired (DLH) cats, Persian and Maine coon cats, with seven males and four females. Similar to dogs and human beings, the majority of oligodendrogliomas are rostrotentorial, involving primarily the cerebrum, although four reported tumors involved structures within the caudal fossa.[16,36,38] Common presenting signs reflect the predominance of lesions affecting the cerebrum, and include seizures, obtundation, mentation changes, and ataxia.

CSF analysis in four cats revealed protein concentrations from 20 to 427 mg/dl and total cell counts from 2 to 45 cells/µl. Interestingly, tumor cells were identified in the CSF of two cats with lesions involving the caudal fossa (Figure 54-3).[36]

MRI usually is characterized by intraaxial mass lesions with variable mass effect, which are hyperintense on T2W images and hypointense to isointense on T1W images. Contrast enhancement usually is present, although variable in nature, and ring enhancement is described in some cererebrally located tumors (Figure 54-4). Although calcification is a frequent finding in human oligodendrogliomas, it is less common in dogs and cats and has not been described on MR or CT images. CT of one cerebral tumor described an intraaxial mass with mild contrast enhancement.[37]

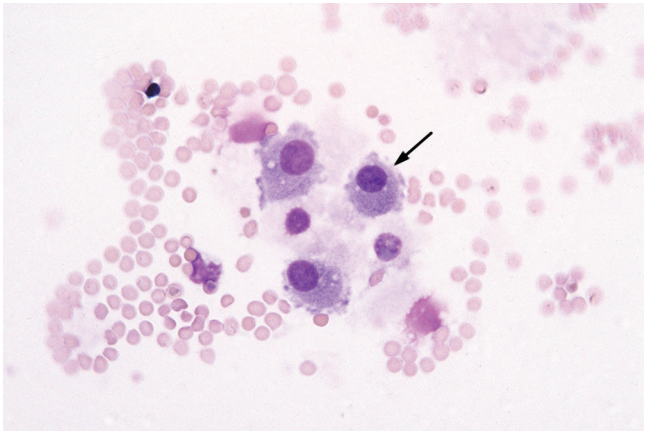


Figure 54-3. Anaplastic oligodendroglioma. CSF cytospin preparation (Wright's stain). Note the large presumptive tumor cells with large, round, dense slightly eccentric nuclei and densely staining cytoplasm *(arrow)*. The other cells are macrophages.

Tumors are described grossly as mucoid or gelatinous (Figure 54-5).[36,41] Involvement of the ventricular system and meninges is common in human beings and dogs, and has been reported in cats[16,36,40]; one cat had two separate lesions.

Histologically, insufficient data exist to determine the prevalence of grade II and grade III (anaplastic) tumors; however, both grades are found in cats.[36] Marked glomeruloid, vascular proliferation is reported in an anaplastic tumor, typical of that found in human and canine cases. The limited immunohistochemical data are similar to that reported in other species, with negative staining for oligodendroglial or myelin markers such as galactocerebroside and myelin basic protein.[36] Ultrastructurally, one tumor was similar to human tumors, except that the feline tumor had a higher concentration of desmosomal junctions and fewer microtubules.[36]

The published treatment of feline oligodendrogliomas has been limited to palliative therapy with glucocorticoids and anticonvulsants, and is anecdotal. The prognosis appears to be poor, because most cats are euthanized within 6 to 8 weeks after diagnosis.

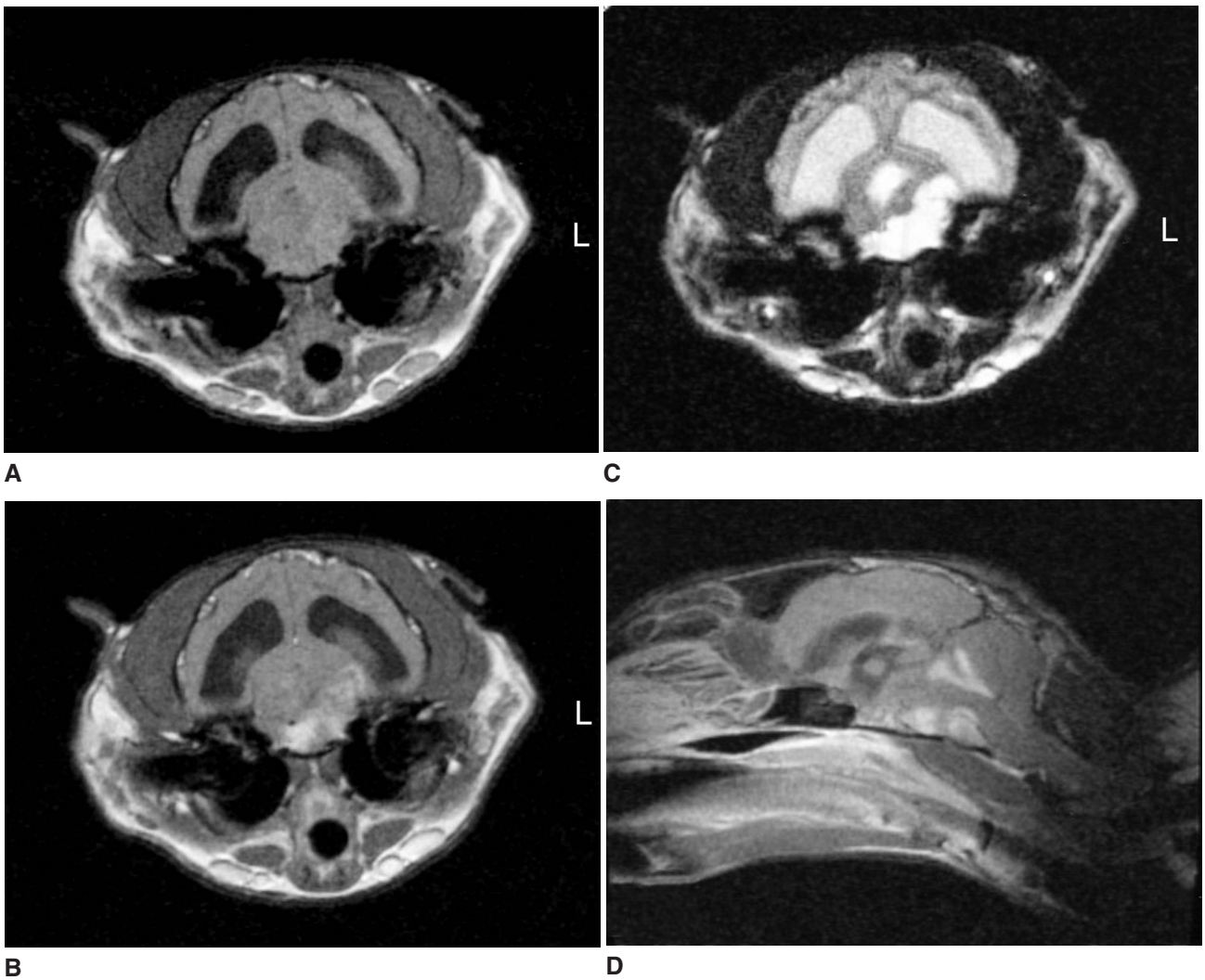


Figure 54-4. Well-differentiated oligodendroglioma on MRI. **A,** T1W image. **B,** T1W image plus contrast. **C,** T2 image. **D,** Sagittal T1 image plus contrast. Two apparently separate, heterogeneously contrast-enhancing masses involving the ventral brainstem and fourth ventricle.

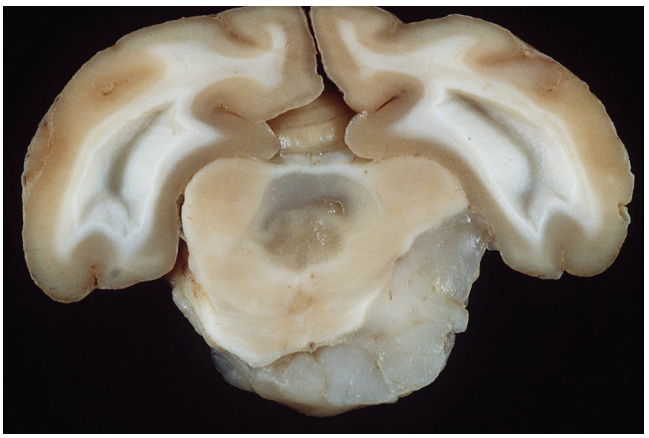


Figure 54-5. Well-differentiated oligodendroglioma, gross pathology transverse section. The tumor has a characteristic gelatinous appearance and is causing marked compression of the adjacent brainstem structures.

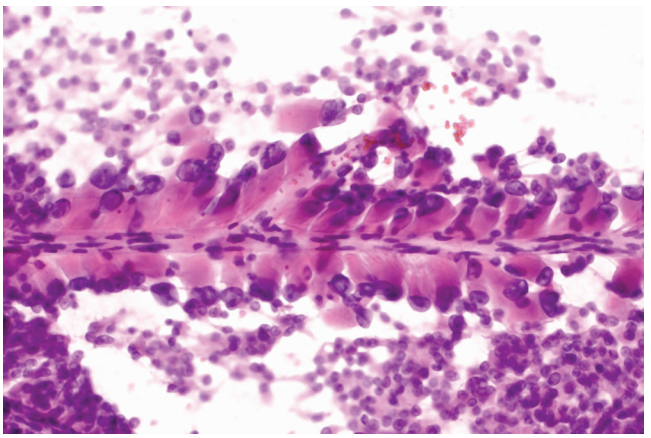


Figure 54-6. Ependymoma; wet fixed smear of brain tissue collected by a CT-guided stereotactic brain biopsy; hematoxylin and eosin stain. The blood vessels appear thickened as a result of the perivascular, palisading layers of ependymal tumor cells. Tumor cells are aligned perpendicularly to the blood vessel with their nuclear pole oriented peripherally. The cytoplasm of the tumor cells is oblong, eosinophilic, and usually unipolar.

CHOROID PLEXUS TUMOR. Intracranial choroid plexus tumors, tumors of the choroid plexus epithelium, are rare: only three reports exist.[16,42,43] Two tumors involved the lateral ventricles, the other the fourth ventricle. Clinical signs included seizures, blindness, and vestibular deficits. No data exist regarding the imaging characteristics or treatment of choroid plexus tumors in cats.

EPENDYMOMA. Reports exist of 19 cats with ependymomas, tumors derived from the ependymal lining cells of the ventricles.* Most cats were 5 years old or older; the ages ranged from 1.5[9] to 13.2 years.[16] Most cats were DSH,† but reports exist of one Siamese,[45] one Burmese,[18] and one DLH.[16]

All tumors were rostrotentorial, except for one in the fourth ventricle[47] and one at the cerebellomedullary angle.[45] The majority of cats had tumors in the third ventricle.[16,18,20,44] Four cats had tumors in the lateral ventricle,[16,25] and one cat had a tumor in the olfactory bulb.[46] Tumors within the third ventricle were most likely to be meningiomas,[16] and thus meningiomas and ependymomas must be considered likely differential diagnoses for mass lesions in the third ventricle in cats. Common neurological signs were seizures, altered consciousness, and diffuse cerebrocortical signs.[16,18,20,46,48] Three cats had vestibular disease.[45,47,48]

Advanced imaging findings, although limited, consistently describe well-circumscribed, uniformly contrast-enhancing lesions with associated ventriculomegaly, presumably secondary to obstruction of CSF drainage.[18,20,47] Given the similar imaging characteristics of meningiomas and their predilection for the third ventricle in cats,[17] ependymoma should be an important differential diagnosis for tumors in this location.

Results of CSF analysis appear variable, with reported values ranging from normal to 95 nucleated cells/μL and 107 mg/dL total protein. A diagnosis of CNS neoplasia was made in one cat based on the presence of clusters of large cells with nuclear hyperchromasia and a highly basophilic cytoplasm.[45]

Histopathological variants include three papillary ependymomas,[18] one tanycytic,[47] and one malignant ependymoma.[48] Obstructive hydrocephalus was a common finding because of involvement of the ventricular system.[16,18,20,44] One cat had an incidental pituitary adenoma.[16] Metastasis of the tumor to regional lymph nodes was reported in one cat.[25]

Diagnosis of ependymoma in one cat was by means of stereotactic CT biopsy[22], and wet-fixed cytology using the smear technique, confirmed by histopathology.[34] Characteristic cytologic features of this papillary ependymoma included prominent thickened, branched blood vessels. The blood vessels were thickened as a result of the perivascular, palisading layers of ependymal tumor cells. Tumor cells were aligned perpendicularly to the blood vessel with their nuclear pole oriented peripherally. Some sheets of single cells with nuclei were round to ovoid. The cytoplasm was oblong, eosinophilic, and unusually unipolar (Figure 54-6).[34]

The lack of information regarding even the natural course of ependymomas makes assessment of the limited numbers of treatments difficult. Three cats treated by craniotomy and mass excision survived for 667 days,[16] at least 7 months,[20] and more than 2 years.[47] Two cats with papillary ependymomas treated with radiation therapy survived 5 months and more than 14 months.[18] However, one cat treated with corticosteroids lived 685 days before euthanasia.[16]

EMBRYONAL TUMORS

Medulloblastoma. Medulloblastomas are tumors believed to arise from the external germinal layer of the cerebellum. One case report exists of a feline medulloblastoma,[49,50] a figure of the tumor histopathology,[15] and a mention of a medulloblastoma in a 3-month-old kitten[25] and in a cat.[12] Signs of hypermetria, leaning, and ataxia reflect the cerebellar origin of these tumors. MRI of one tumor was hypointense on T1W images, hypointense and hyperintense on T2W images, and had slightly heterogeneous contrast enhancement. Results of surgical resection via a suboccipital craniotomy were disappointing. The cat apparently recovered well from surgery but died on day 23 postoperatively.[49,50]

Supratentorial Primitive Neurectodermal Tumor (PNET)

Olfactory Neuroblastoma. Thirteen feline olfactory neuroblastomas, tumors thought to arise from nasal neuroepithelial precursors, have been reported.[16,25,51-55] Two cats in one case

*References 6,7,9,15,16,18,20,25,33,44-48.
†References 6,16,18,20,44,47.

series[52] were reported previously in another study.[51] All tumors involved the nasal cavity with erosion of the cribriform plate and extension into the cranial vault. Most tumors invaded the brain. Sneezing, dyspnea, coughing, and/or nasal discharge, together with neurological signs of cerebrocortical dysfunction, were the most common presenting signs.[16,51,53,54] All cats had neurological abnormalities except for one patient.[51]

MRI of two tumors had extraaxial mass lesions with indistinct borders, mass effect, and marked peritumoral edema, with erosion of the cribriform plate.[17] Tumor on T1W and T2W images was homogeneous but variable in intensity; however, both had marked heterogeneous contrast enhancement.

At necropsy, all cats had tumors in the nasal cavity that extended through the cribriform plate into the cranial vault. Tumors invaded the dura mater and cerebrum, except in one cat in which no brain invasion occurred.[16] Most tumors had associated hemorrhage and necrosis. Metastasis was present in a submandibular lymph node in two cats,[51,53] and multiple neoplastic nodules were in the subarachnoid space, over the brain in another cat.[53] One cat was treated by excisional biopsy and palliative corticosteroids, but was lost to follow-up after 30 days.

In one study, three cats had type C retroviral particles found within the tumor cells, and in one cat, viral particle budding was noted. We suggest that a causal relationship may exist between FeLV infection and the genesis of olfactory neuroblastomas.[53] However, not all cats with olfactory neuroblastomas are FeLV-positive.

Germ Cell Tumors

TERATOMA. Teratomas are tumors derived from pluropotent cells that contain elements of different tissue types. One case report exists of a teratoma (thalamus), and dermoid cyst (frontal lobe), and hydrocephalus in a 4-month-old DSH kitten. The kitten had a history of seizures, progressive gait abnormalities, and visual impairment, and had facial deformities. Facial deformities consisting of a broad face, prognathism, depressed nasal bridge, and bulging frontal bones were noted on physical examination. Neurological abnormalities consistent with bilateral forebrain and brain stem disease were present. The kitten was euthanized without treatment.[56]

Tumors of the Sellar Region

CRANIOPHARYNGIOMA. One abstract reports a craniopharyngioma, an epithelial neoplasm of the sellar region, in two cats: a 9½-year-old male castrate (MC) Chinchilla cat, and a 7-year-old MC American short-haired cat. Both cats had a history of respiratory disease (wheezing, open mouth breathing, and nasal discharge). The tumors appeared to be aggressive, with invasion of the nasopharynx and tympanic bulla, or lysis of the skull base. Both cats had MRI of the brain, but descriptions were not provided.[57]

Lymphomas and Hematopoietic Neoplasms

MALIGNANT LYMPHOMAS. Lymphoma, a malignant lymphoid neoplasm, is the most frequently diagnosed neoplasm in cats[4] and the second most frequent CNS tumor.[6,16] Lymphoma affects the brain less frequently than the spinal cord, cranial nerves, or peripheral nerves.[6,25] CNS lymphoma is classified as primary when no evidence exists of systemic lymphoma,[16,58,59] but usually it is part of a multicentric disease.[6,60] One study described primary intracranial lymphoma in 35 per cent of the cats with lymphoma.[16] Most reports group primary CNS lymphoma and multicentric lymphoma with CNS involvement together, and little separate data exist.[16,17,25,37,59]

Determining whether feline primary CNS lymphoma is predominantly of B- or T-cell in origin is impossible based on the single immuno-typed T-cell case.[58] We have diagnosed primary B-cell and T-cell intracranial lymphoma. The association between CNS lymphoma and FeLV or FIV infection is not proven.[16] Although an association exists between renal and CNS lymphoma,[61] no information is available to determine whether this includes an association specifically with intracranial lymphoma.

Cats with primary CNS lymphoma or multicentric lymphoma ranged in age from 0.4 to 19.4 years of age,* with no sex predisposition. Most cats were DSH, but a Siamese cat[62] and a Persian cat[58] also were affected. The most common neurological signs included ataxia, altered consciousness, seizures, blindness, upper motor neuron paresis, and cranial nerve deficits.[16,25,58-60,62] Three cats were being treated for lymphoma when neurological signs developed.[59]

MRI of intracranial lymphoma may show multiple or solitary lesions that may be intraaxial or extraaxial. Lesions usually are isointense to hypointense on T1W images and hyperintense on T2W images with moderate to marked peritumoral edema. Uniform contrast enhancement is common, and additional features such as meningeal involvement, infarcts (secondary to intravascular lymphoma),[62] and thickening of the skull may be recognized.[17] Six cats had solitary ring-enhancing lesions after IV contrast administration on CT imaging.[59]

CSF analysis may show mixed cell pleocytosis and/or elevated protein concentrations or may be normal. Absence of malignant lymphocytes in CSF does not rule out CNS lymphoma. Neoplastic lymphocytes are identified in 50 per cent of CSF samples on which a cytological examination was performed.[16,59]

The ideal treatment for intracranial lymphoma is not known. One study of cats with CNS lymphoma showed clinical improvement with surgery, radiation therapy, and chemotherapy.[59] The use of chemotherapeutic drugs that have increased penetration of the blood-brain barrier such as lomustine (CCNU) and cytosine arabinoside has been recommended anecdotally as additions to standard lymphoma chemotherapeutic protocols; however, their efficacy has not been proven.[63] In our experience, the prognosis for intracranial lymphoma is guarded. Survival times generally are less than 6 months.[59]

PLASMACYTOMA. A plasmacytoma is a tumor of malignant plasma cells. One case report exists of an intracranial plasma cell tumor in a 6-year-old male neutered DSH cat presenting with a 1-week history of staring into corners and circling compulsively. The neurological deficits were localized to the left prosencephalon. On CT imaging, a 1-cm contrast-enhancing lesion that was associated with the left lateral ventricle was noted. Also noted were a mass effect and marked contrast enhancement of the wall of the lateral ventricle. Neoplastic cells were identified in CSF. The cat did not improve with

*References 6,16,25,58-60,62.

corticosteroids and was euthanized after 2 weeks. A complete necropsy was not done and thus multiple myeloma could not be ruled out. The brain was evaluated histologically. A mass was present in the caudate nucleus that invaded the left ventricle, and the left ventricle was full of blood.[64]

Secondary Intracranial Neoplasia

Pituitary Tumors

Pituitary gland tumors, tumors of the secretory cells of the adenohypophysis or neurohypophysis in cats, are an uncommon cause of neurological dysfunction. They arise from either the neurohypophysis (primary neuroectodermal tumor) or the adenohypophysis (nonneural tumors). Tumors of the adenohypophysis may be divided further depending on whether they arise from the pars distalis or pars intermedia; whether they are endocrinologically functional or nonfunctional; and whether they are adenomas or carcinomas. Published literature regarding feline pituitary tumors is frustrating because of the lack of histological confirmation of tumor type. A presumptive diagnosis often is made based on presence of endocrinological disease and a mass in the region of the pituitary gland. Therefore making only general statements is possible regarding clinical aspects of these tumors in many cases. The majority of tumors occur in older animals (older than 8 years), with no obvious breed predisposition. Domestic short-haired cats and other breeds including DLH, Persian, Abyssinian, Russian blue, and Siamese have been reported with a variety of tumor types.

TUMORS OF THE ADENOHYPOPHYSIS. Endocrinologically active tumors of the adenohypophysis are generally one of two types in cats: (1) corticotroph (chromophobe) adenomas (adrenocorticotrophic hormone [ACTH] secreting)[65-71] and (2) acidophil adenomas (growth hormone [GH] secreting).[72-79] A double adenoma with ACTH and GH secreting tumors also has been reported.[80]

Cats generally present with clinical signs of endocrinological disease, namely pituitary dependent hyperadrenocorticism (PDH) or acromegaly. Many also have concurrent diabetes mellitus that often is resistant to insulin therapy. Neurological signs are an uncommon early presentation but may develop later in the disease course as the tumor size increases. Many affected cats die from complications relating to the endocrine disease before neurological signs become manifest. A clear preponderance of male cats exists relative to females with acidophilic adenomas and acromegaly, and although a greater number of male cats with chromophobe adenomas apparently exists, the number of definitively diagnosed cases is small.

Pituitary carcinomas occur less frequently than adenomas in cats. Although carcinomas may be less likely to be endocrinologically active, several reports exist of functional tumors.[68,81] Nonfunctional adenomas appear to be less common tumors than functional adenomas, with few reported cases.[82,83] Because of the limited available data, to determine whether nonfunctional feline pituitary carcinomas[81,84,85] are more common than functional carcinomas is impossible.

Whether nonfunctional tumors are adenoma or carcinoma, cats are much more likely to present with primary neurological signs. Neurological deficits relate to the anatomical location of the pituitary gland and commonly involve diencephalic signs such as mentation changes, circling, and visual and pupillary light reflex deficits (mydriasis); seizures may occur in advanced tumors.[81-86] Secondary compression of normal pituitary structures may result in impaired vasopressin release and central diabetes insipidus.

TUMORS OF THE NEUROHYPOPHYSIS. These are rare in all species—a single case of a cystic pituicytoma has been reported in a 7-year-old FS Siamese cat.[86] The cat presented with neurological signs of decreased mentation and loss of the oculocephalic reflex. Tumors arise from the pituicyte supporting cells in the neurohypophysis

A presumptive diagnosis of a pituitary tumor typically is based on clinical signs, whether endocrinological or neurological, together with advanced imaging techniques. Definitive diagnosis can be made only based on biopsy of tumors, either surgically[65,80] or by stereotactic needle biopsy.[22] Biopsy of larger, endocrinologically inactive masses may be more important to rule out other potential tumors such as meningioma and lymphoma, or to determine whether a pituitary tumor is an adenoma or a carcinoma.

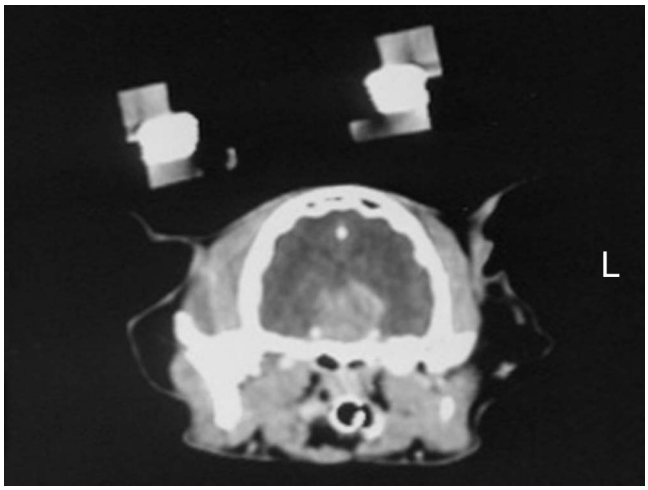
Imaging characteristics and size of the normal feline pituitary gland have been published for CT[65,87] and MRI,[88] and are useful in determining the presence of relatively small tumors. Dynamic contrast studies also may help to determine location of tumors within the pituitary gland.[80] The pituitary gland has a variable mixed signal on MRI T1W images with hyperintense signal in the caudal one third of the gland in 50 per cent of cats (thought to reflect neurosecretory granules in the neurohypophysis). The normal pituitary gland usually enhances uniformly on post-contrast CT images and MRI. The imaging characteristics of pituitary tumors can vary. Some tumors may be hyperattenuating on pre-contrast CT images.[73,74] The majority are contrast-enhancing on CT* and MRI[17,78,81,83]; however, the degree and homogeneity of the enhancement can be variable (Figure 54-7, *A*). In our experience, speculating whether a suspected tumor is a carcinoma or adenoma based on characteristics such as how well defined is the mass, or how uniform is the enhancement, can be misleading, and examples of well-circumscribed carcinomas[85] and apparently invasive adenomas[83] can be found in the literature.

Treatment choices are based on whether the tumor is endocrinologically functional and the tumor size. Medical treatment of acromegaly has been attempted using bromocriptine, the somatostatin analogue octreotide, and the dopamine agonist L-deprenyl, with mixed results. Medical treatment of PDH with mitotane and inhibitors of steroid enzyme pathways such as metyrapone, ketoconazole, and trilostane generally has been disappointing.

External beam radiotherapy (^{60}Co teletherapy, linear accelerator) has shown variable results in terms of reduction of endocrine function and tumor size; however, apparently beneficial responses have been reported in many cases with survival times from several months to years in successful cases.[68,75,81,84,89]

Surgical treatment of PDH may include bilateral adrenalectomy or transsphenoidal hypophysectomy.[65,78,80] Postoperative complications of adrenalectomy may be life-threatening, and although hypophysectomy is a surgically challenging procedure, also with potential postoperative complications, results in cases of feline PDH have been encouraging: several cats survived for years with minimal complications. This may be

*References 65,74,75,80,81,84,85.



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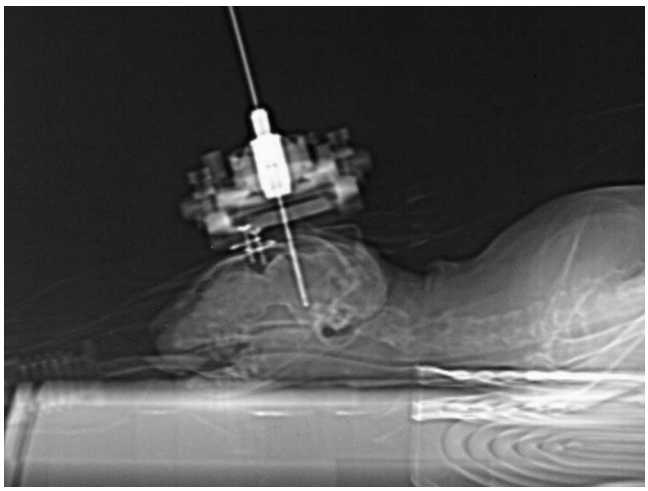

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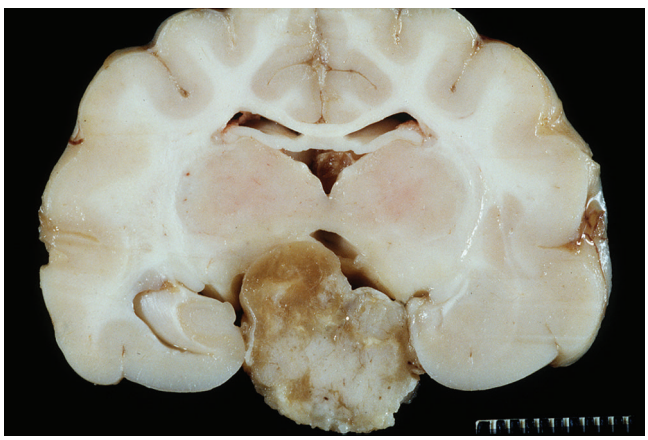

C

Figure 54-7. Corticotroph (chromophobe) adenoma (nonfunctional) from a 6-year-old female spayed cat with a 1-year history of seizure-like episodes and no endocrinological abnormalities. **A,** CT post-contrast image: a uniformly contrast-enhancing mass with a somewhat irregular border is present ventral to the thalamus in the region of the pituitary gland. **B,** Stereotactic CT-guided brain biopsy (modified Pelorus Mark III system). The biopsy needle can be seen within the mass lesion (the mass is not visible in this image). **C,** Gross pathology showing a large well-circumscribed tumor compressing the overlying thalamus and third ventricle.

the treatment of choice for all small tumors, if available. Cats with large tumors, whether adenoma or carcinoma, are not surgical candidates, and preferred treatment generally is radiation therapy (Figure 54-7, *C*).

Prognosis for the various tumor types is difficult to assess based on currently available data. Many tumors are slow growing, and prognosis is more dependent on endocrinological complications such as uncontrolled diabetes mellitus, infections, renal failure, cardiomyopathy, and discouraged owners. Larger nonfunctional tumors presenting with neurological signs are likely to have a poorer prognosis. Little informative data are available; however, some patients may respond to radiation treatment and palliative corticosteroid therapy. Whether prognosis for carcinomas and adenomas is significantly different is unclear.

Aural Tumors

Malignant middle ear tumors are reported infrequently in cats.[90] The most common malignant middle ear tumor of cats is the squamous cell carcinoma, although adenocarcinoma, fibrosarcoma, adenosquamous carcinoma, anaplastic carcinoma, lymphoblastic lymphosarcoma, papillary adenoma, and ceruminous gland adenocarcinoma also have been reported. Any of these neoplasms have the potential to extend to involve the brain. Intracranial extension of middle ear neoplasia is rare, but has been reported in cats with papillary adenoma, adenocarcinoma,[91,92] and squamous cell carcinoma.[93]

Most cats with extension of middle ear neoplasia had peripheral vestibular disease, but one cat was normal neurologically.[91,92] CT is the imaging modality of choice to delineate bony lysis or production involving the cranial vault; however, extension of soft tissue masses often is visualized only after intravenous contrast or on MRI. Lesions may be homogeneously contrast enhancing or ring enhancing after IV contrast administration (Figure 54-8).

Two cats[91] (one with an adenocarcinoma and one with a papillary adenoma) underwent bulla osteotomy and craniectomy. Both cats had prolonged survivals (630 days; at least 840 days, respectively); much longer than other reports of cats with middle ear neoplasia. Other cats with middle ear neoplasia with or without brainstem extension were treated by means of bulla osteotomy and euthanized within 3 months of diagnosis.[92,94] The value of adjunctive chemotherapy or radiation therapy for invasive middle ear tumors currently is unknown. Middle ear tumors should be considered as a differential diagnosis in old cats with chronic otitis, peripheral or central vestibular signs, Horner's syndrome, or pain on opening the mouth.

Nasal Tumors

Intranasal tumors are rare tumors in cats.[4,10,11] They appear to be more frequent in male cats, with a male:female ratio of 2:1 reported in one study.[95] Many different histological types of intranasal tumors exist[95]; however, most are malignant and locally invasive, and metastasis to the local lymph node and lungs can occur.[52] Local invasion through the cribriform plate is reported, in addition to brain infiltration.[16,37,52,96] In addition to signs of upper respiratory disease, reported neurological signs in cats with nasal tumors that have invaded the cribriform plate include seizures,[52] circling, and altered mentation.[16]

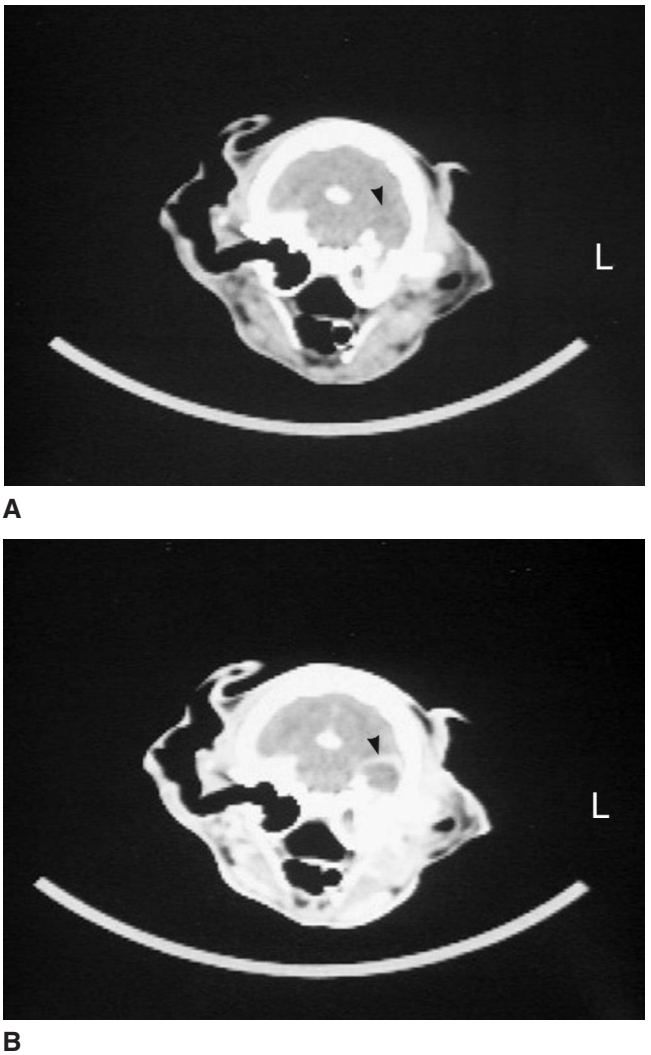

Figure 54-8. Middle ear tumor (papillary adenoma). Transverse CT **(A)** precontrast and **(B)** post-contrast, at the level of the tympanic bulla. Note the hypoattenuating lesion *(arrowhead)* at the level of the pyriform lobe that is ring-enhancing post-contrast. The left ear canal and bulla are filled with a soft-tissue or fluid density.

The preferred treatment for most feline nasal tumors is radiation therapy.[52,96] However, the relative benefits of surgery and radiation therapy for nasal tumors that have invaded the cranial vault, with compression and invasion of the brain, is unknown.

Metastasis

Intracranial metastasis is reported infrequently in cats. In a recent study, the frequency of intracranial metastasis was 5.6 per cent.[16] Types of metastatic tumors reported in the brain include pulmonary,[16] mammary,[97] and endometrial[98] adenocarcinoma; squamous cell carcinoma; fibrosarcoma; malignant fibrous histiocytoma; hemangiosarcoma; unclassified sarcoma; unclassified adenocarcinoma[16]; sweat gland adenocarcinoma[99,100]; malignant melanoma[101]; and lymphocytic leukemia metastatic to the meninges.[102]

Most tumors are located rostrotentorially and commonly involve the cerebral cortex. Neurological deficits reflect the location of the lesion(s). Little information is available regarding treatment, because most cats are diagnosed postmortem or euthanized once metastatic disease is suspected.

EXPERIMENTAL TUMORS

A variety of techniques have been used in the generation of experimentally induced brain tumors in cats for the study of tumor biology and therapeutic intervention. Common methodologies include the use of chemical carcinogens, radiation, oncogenic viruses, and transplantation of glial tumor cell lines.

Interestingly, cats appear to be relatively resistant to carcinogens such as the polycyclic hydrocarbons and also to induction of tumors with simian vacuolating virus (SV 40).[103] No established feline derived brain tumor cell lines are available to our knowledge; however, orthotopic brain tumors have been created in immunocompetent cats using rat glioma cell lines (C6, F98)[104,105] and in cyclosporine-treated, immunosuppressed cats using human glioma cells (D54).[106] Tumors have many characteristics of spontaneous tumors such as necrosis, neovascularization, and local invasion; however, most are well-circumscribed masses, and immunocompetent cats reject tumors after approximately 4 weeks.

FUTURE DIRECTIONS IN FELINE BRAIN TUMORS

Diagnostics

With widespread availability of advanced imaging techniques, the number of cats diagnosed with intracranial mass lesions has increased significantly. Imaging characteristics of specific tumor types have been published; however, imaging does not provide a specific diagnosis. Definitive diagnosis is confirmed based primarily on the results of biopsy, histopathology, and immunohistochemistry. A definitive diagnosis may be possible if neoplastic cells are noted cytologically in the CSF.[36,59,64]

Biopsy of primary brain tumors presents a number of location-specific problems, involving primarily the relative inaccessibility of lesions, together with the significant risks associated with surgical biopsy in many cases. Although limited in availability at this time, recent advances in the development of stereotactic CT-guided biopsy of tumors have done much to improve the likelihood of obtaining an accurate antemortem diagnosis, which allows for a more appropriate and informed approach to therapeutic planning (see Figure 54-7, *B*).

Over the past 15 to 20 years, a large effort has been put forth to understand the specific molecular abnormalities underlying the development and progression of human primary brain tumors. Many of these abnormalities involve tumor suppressor genes, oncogenes, and pathways involved in cell cycle regulation and angiogenesis. Defining tumors in terms of their molecular characteristics has allowed for further classification of apparently histologically identical tumors into distinct subgroups. This has had a major impact on the ability to predict survival times and response to conventional therapies. For example, many human oligodendroglial tumors exhibit loss of chromosomes 1p and 19q. Loss of 1p or combined loss of 1p and 19q is associated with increased chemosensitivity and survival. Overexpression of the epidermal growth factor receptor (EGFR) and insulin-like growth factor receptor (IGF1R) in gliomas is associated with radioresistance; similarly, overexpression of the vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) is associated with a poor prognosis.

The ability to predict response to treatment based on the presence or absence of specific molecular markers has taken human clinical pathology/histology to a new level, and helps to select appropriate patients for specific treatments. The detection of these new molecular markers also helps to assess efficacy of therapeutic regimens more realistically, which may have appeared ineffective when applied to a "mixed" population of uncharacterized and potentially inappropriate tumors.

Treatment Modalities

In general, conventional therapeutic approaches to brain tumors in people and animals have involved a combination of surgical debulking/resection, chemotherapy, and radiation therapy. With the exception of meningiomas in cats, the prognosis for the majority of primary brain tumors (particularly intraaxial tumors), even with conventional treatment, is guarded to poor. Survival with symptomatic treatment alone often is measured in terms of weeks in most cases, particularly in cats with astrocytomas or oligodendrogliomas. A large body of clinical data exists in human medicine pertaining to the relative efficacy of these therapies for specific tumors, together with the expected prognosis. Very little similar objective information is available for cats, even relating to the normal progression of brain tumors in the absence of treatment. Small case study series, lack of antemortem (or postmortem) diagnoses, differing treatment plans, the high degree of variability associated with an end point (often defined by euthanasia), and variation in clinical severity at presentation have made the comparison of feline and human data very difficult.

Even in human medicine, the progress made over the last 15 to 20 years in treatment strategies for the more malignant brain tumors has been modest at best, and prognosis for high-grade tumors such as astrocytoma is still poor: median survival time is 4 to 16 months. Temozolamide (Temodar) is the only new chemotherapeutic agent that has been approved for use in human brain tumors since the approval of BCNU and CCNU almost 30 years ago. Survival gains have been modest and the cost and availability of Temodar are likely to preclude its use in veterinary practice at this time.

The advent of stereotactic radiosurgery (either Linac or Gamma knife) has had a significant impact on brain tumor treatment in selected clinical situations. Delivery of high doses of focused radiation to a precisely defined target, usually in a single dose, may be particularly useful in the treatment of small tumors in patients at high risk for conventional surgery because of tumor location, secondary medical illness, or tumor recurrence. The potential benefits of a noninvasive, single dose (and therefore anesthetic) treatment modality in veterinary medicine are obvious, and radiosurgery has been described in the dog[107] but not in the cat at this time.

Because of the relatively poor response of many human primary brain tumors to conventional therapies, many novel approaches have been developed. Many of these approaches target the molecular abnormalities known to be present in specific tumors such as replacing abnormal or absent tumor suppressor gene function (e.g., TP53), or inhibiting growth factors known to be important in angiogenesis or tumor growth (e.g., VEGF, EGF). If appropriate pathways are present, such targeted treatments can be extremely effective, as has been shown in the remarkable success of ST1571 (Gleevec) in the treatment of chronic myeloid leukemia (ST1571 targets the constitutively activated BCR-ABL tyrosine kinase receptor). Many similar treatments currently are in development and clinical trials in human brain tumor patients. Additionally, overexpression of markers specific to brain tumors can be used to target nonspecific therapeutics such as toxins or more conventional chemotherapeutic agents. Gene therapy using viral vectors such as adenovirus, retrovirus, and adeno-associated virus also has been assessed in both experimental and clinical tumors. The ability of many viruses to transduce tumor cells (or normal brain) depends on many factors including appropriate cell surface targets. Generation of promoter-specific viral constructs also adds an additional targeting step helping to ensure that therapeutic gene expression occurs only in the appropriate cell types.

No published data document the molecular characteristics of feline brain tumors. Because of the relatively low incidence of brain tumors in cats versus dogs, and the generally favorable response of the most common feline tumor (meningioma) to surgery, initial efforts to elucidate molecular pathways of brain tumors in domestic animals likely will concentrate on dogs. Sequencing of the feline genome is planned in the near future, and this will help enormously in promotion of the basic research to ensure that the veterinary profession is able to benefit from current and future advances in human brain tumor therapy.

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Chapter 55

Seizure Disorders and Treatment Options

Karen L. Kline

In order to institute appropriate therapeutic strategies for seizure management in cats, the clinician must be aware of the pathophysiology and associated disease processes. Seizure disorders in cats have been reviewed in previous literature.[1-9] A seizure is a clinically detectable manifestation of paroxysmal, excessive, and synchronous discharges of a population of hyperexcitable cerebral neurons. Classification schemes are reviewed for determining seizure type and differential diagnoses. Acquired causes for seizures are emphasized to assist with diagnosis and treatment of seizure disorders in cats.

CLASSIFICATION OF SEIZURES

Further classification of seizure type relies on appropriate use of the term *epilepsy* (recurrent seizures). Recurrent seizures are defined more broadly as epilepsies. Podell, Fenner, and Powers adopted a nomenclature scheme from human epilepsies based on identifiable causes.[10] Primary epileptic seizure (idiopathic) is the term used if an underlying cause cannot be identified. If seizures result from a structural lesion, they are defined as secondary epileptic seizures. The term *reactive epileptic seizure* is used when the normal brain reacts to transient systemic insult or physiological stresses; these seizures are not considered recurrent. Epilepsies also are described as *asymptomatic* (primary, idiopathic) and *symptomatic* (secondary).[11] I use the terminology of primary and secondary epilepsies for this discussion. Secondary epilepsy is common in cats, and appropriate diagnostic tests are necessary to determine the underlying cause.[2,3,5,6]

Primary epilepsy implies recurrent episodes of seizure activity associated with a primary functional cerebral disorder (having a physiological or biochemically related genetic basis). Typically, these seizures are tonic clonic and generalized with no identifiable structural brain lesions. Physical and neurological examinations are normal. Advanced imaging and CSF analysis results are normal. Incidence of primary epilepsy in cats is low when compared with that of dogs.

Secondary epilepsy (also named symptomatic, acquired, or structural) implies recurrent seizure activity caused by acquired but inactive brain diseases that occur after traumatic, ischemic, and encephalitic events. According to some authors,[2,3,9] the term epilepsy should be restricted to recurrent seizures resulting from nonprogressive intracranial causes of either a structural or functional nature. Others classify secondary epilepsy (symptomatic) as recurrent episodes of seizure activity associated with an underlying structural disorder such as inflammation, trauma, ongoing hypoxia or ischemia, or neoplasia.[2,3,9] In cases of secondary epilepsy, partial seizures (focal or complex partial with or without secondary generalization) are observed more commonly and may be accompanied by an abnormal neurological examination with or without lateralization. Secondary epilepsy is thought to be more common in cats than primary epilepsy.[2] *Reactive seizures* arise as a consequence of extracranial metabolic or toxic insults.

CLINICAL SIGNS

Seizure type can be characterized as (1) generalized with major motor activity (i.e., generalized tonic-clonic events), (2) partial with subtle motor manifestations (mild generalized or partial seizures [i.e., limb, facial, or whisker twitching]), or (3) nonmotor (psychic or autonomic activity [i.e., tail chasing, floor-licking, vocalizing]).

Seizures in cats, regardless of the cause, manifest themselves in different ways and are more variable in clinical presentation than in dogs.[1-9] The owner may not notice the ictal phase or actual seizure event readily until the signs are more obvious. The aura or preictal phase may comprise subtle behavioral changes that include aggressiveness, pacing, crying, restlessness, hiding, unusual affection, salivation, frantic running, hissing, growling, and anxiety.[2-6] The aura may last seconds to days, but usually lasts for several minutes.

The ictal phase can be classified further according to seizure type. *Generalized* and *partial* seizures occur in cats. *Generalized seizures* (tonic-clonic or grand-mal seizures) manifest as loss of consciousness, recumbency, and tonic-clonic motor activity. The major motor activity can consist of generalized tonic movements with the limbs in rigid extension and pur-

Figure 55-1. Feline seizures can be comprised of violent motor activity, autonomic release, in addition to facial twitching, salivation, kicking, piloerection, and chewing.

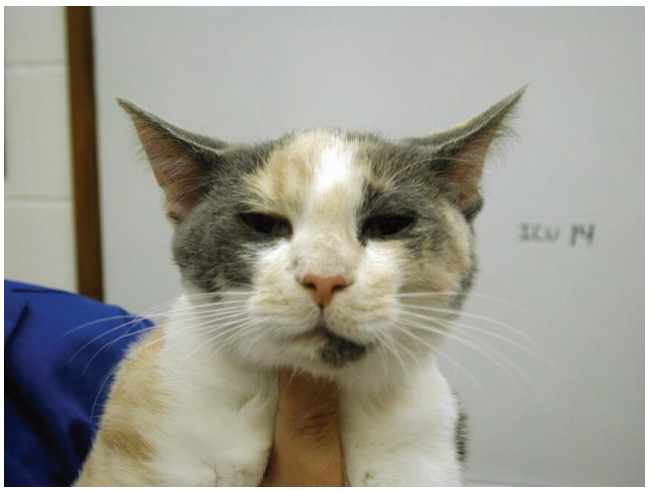

Figure 55-2. Postseizure or postictal cats may appear blind and exhibit inappropriate behavior for a short interval after the seizure event.

poseless limb movements and paddling. Opisthotonus and claw extension in addition to mouth-chomping and pupillary dilation also may be observed. At times, tonic flexion (emprosthotonus) is observed, which may be followed by moderate to severe muscle twitching (clonic phase). The patient may not have loss of consciousness during this type of event. Sometimes generalized seizures can be violent. The cat may jump up into the air as if it were thrown and propel itself forward and from side to side. Autonomic release (urination and defecation) usually accompanies the motor activity in addition to facial twitching, salivation, kicking, piloerection, and chewing (Figure 55-1). Self-inflicted trauma may be observed to include contusions, excoriations, biting of the tongue, or avulsion of the claws. Cats also may exhibit mild or nonconvulsive seizures, which are manifested by impaired consciousness, pupillary dilation, bilateral facial twitching, muscle spasms of the head and neck, and possibly, autonomic release.[2-6,9] The ictus usually lasts from seconds to minutes and sometimes can progress to status epilepticus.

The postictal period is similar to that observed in dogs and can last from seconds to days. This period can manifest as confusion, aimless wandering, pacing, blindness, increased hunger, and changes in sleep/wake patterns (Figure 55-2).

Partial seizures are subdivided into *complex partial seizures* and *simple partial seizures*; complex partial seizures are common in cats. Such events often have lateralizing signs preceding or during the ictus. Cats with complex partial (psychomotor) seizures manifest impaired consciousness with stereotypic motor activity (that may lateralize) and behaviors.[5,6,9] These activities include turning of the head to one side, chewing motions, transient staggering, and ventral flexion of the head. These episodes often are preceded by a short, piteous cry, intermittent episodes of aggression or fright, hissing, growling, raising of a single limb (repetitive movements), tail piloerection, and transient periods of incoordinated, frantic running or bizarre aimless movements. Owners describe their cats as acting like they are "possessed," or in a trance as if they were hallucinating. Compulsive activities such as biting, self-excoriation, and circling can be observed. These episodes of bizarre behavior are distinguished from behavioral issues by the presence of facial twitching, salivation, or a secondary seizure generalization.

Simple partial seizures are characterized by near-normal or normal mentation and the appearance of unilateral motor signs involving a part of or all of the body. Cats with focal seizures often twitch the eyelids, whiskers, and/or ears either in combination or separately. Head-shaking may occur and be accompanied by body jerking. Salivation, urination, and pupillary dilation are transient signs. Continuous vocalization and a brief rise in body temperature can be observed. Hyperthermia ensues as a result of continuous motor activity that can last from minutes to hours. Partial motor seizures are variable in clinical presentation and difficult to recognize for the untrained eye.[2,5,6] Also, partial seizures may progress to tonic-clonic or generalized seizures. Seizures of this type may be more difficult to control because of the prolonged ictal phase. Up to one third of cats have seizures that progress to status epilepticus or cluster seizures. Cats also may have an atypical presentation of nonconvulsive seizures that go undetected for prolonged periods.[2,6,12,13] Requesting the pet owner to videotape these episodes is helpful to document the severity and type of seizure.

DIFFERENTIAL DIAGNOSES

Signalment and initial examination assist with establishment of differential diagnoses. Differential diagnoses for seizure disorders in young cats (less than 4 years of age) include congenital, inflammatory, infectious, toxic, and metabolic causes, whereas in the older cat (over the age of 5), common differential diagnoses include vascular, neoplastic, and infectious inflammatory causes. Exceptions to this guideline do occur; therefore, causes for seizures are assessed on an individual basis.

Secondary or reactive epilepsies are common in cats, whereas in dogs, primary (idiopathic) epilepsy is considered a common differential diagnosis.[2,5,6,9] However, reports have described that at least 50 per cent of cats studied were considered as idiopathic epileptics because the seizure etiology could not be determined after exhaustive diagnostic testing.[1,3] In other words, an underlying cause is suspected but cannot be proven

antemortem. Careful inspection of the brain postmortem may reveal the symptomatic cause.

For the purposes of this discussion, origins of secondary epilepsies in cats are subclassified as *extracranial* or *intracranial*. A disease process of extracranial cause disrupts the normal physiology of the brain. Examples include metabolic disorders, nutritional disturbances, and toxins (Table 55-1). A disease process of intracranial origin disrupts or changes the normal architecture of the brain tissue or vasculature. Examples include neoplasia; inflammatory, infectious, or vascular lesions; congenital anomalies; degenerative disorders; and trauma.

Extracranial Etiologies

Hepatic Encephalopathy

Seizures associated with clinical signs of hepatic encephalopathy (HE) in cats occur relatively infrequently.[2,5,6,14,15] Causes of HE include portosystemic shunting, severe hepatic lipidosis, cholangitis/cholangiohepatitis (either primary or secondary to infectious diseases such as feline infectious peritonitis), neoplasia, and end-stage liver disease. A myriad of metabolic imbalances and toxic substances act synergistically to produce neurological signs. The major contributor to the clinical signs observed is hyperammonemia[5,14] (see Chapter 11). Mercaptans, indoles, and aromatic amino acids also play a role in abnormal neurotransmission and generation of false neurotransmitters available for use in the brain. Increases in excitatory neurotransmitters such as glutamate and alterations in endogenous benzodiazepines have been documented in animals with seizures. High cerebral concentrations of these benzodiazepine-like substances may explain the relative rarity of seizures in cats with HE. The exact role of these metabolic by-products in the generation of seizures has not been determined (Figure 55-3).

Depending on the underlying cause of the HE, most cats will be systemically ill. Neurological signs are consistent with a diffuse forebrain localization and commonly are episodic in onset. If seizures occur, they are accompanied by long periods of abnormal behavior and mentation. Aberrant or bizarre behavior, dementia, aggression, ataxia, head pressing, propulsive circling, blindness, mydriasis, ptyalism, and partial or generalized seizures, may be observed. In cases of portosystemic shunts, the aforementioned signs may occur within hours after eating and often are accompanied by severe ptyalism. Excess salivation is not a manifestation of seizure activity but is theorized to be due to cerebrocortical-mediated abnormal

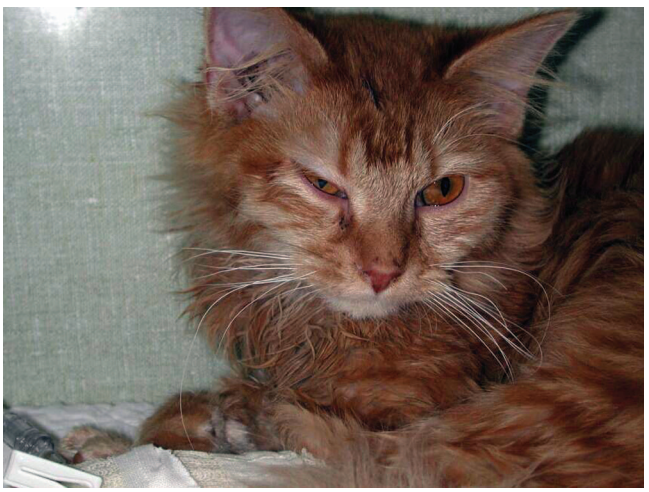

Figure 55-3. A metabolic cause of seizures in young cats is hepatic encephalopathy secondary to an extravascular portosystemic shunt.

Table 55-1 | **Etiology of Feline Seizures**

INTRACRANIAL
Neoplasia
Meningioma
Lymphoma
Glial tumors
Pituitary adenoma/adenocarcinoma
Choroid plexus adenoma/adenocarcinoma
Metastatic
Inflammatory/Infectious
Toxoplasmosis
Cryptococcosis
Blastomycosis
Cladosporium
FIP
FeLV/FIV
Rabies
Aberrant parasite migration (*Cuterebra* larvae or adult *Dirofilaria immitis*)
Other unknown viral causes (nonsuppurative meningoencephalitis)
Vascular
Ischemic encephalopathy
Hypertension
Embolism secondary to underlying cardiac disease
Thromboembolism of unknown cause
Polycythemia (relative versus absolute – primary versus secondary)
Degenerative/congenital/anomalous/malformation
Storage diseases
Hydrocephalus
Traumatic
Immediate
Delayed (posttraumatic epilepsy)
EXTRACRANIAL
Metabolic
Hepatic encephalopathy
Lipidosis
Portosystemic shunt
Cirrhosis/fibrosis
Neoplasia
Cholangitis/cholangiohepatitis
Hyperthyroidism
Hypocalcemia
Primary hypoparathyroidism
Post-thyroidectomy
Hypoglycemia
Insulin-secreting tumor (insulinoma)
Insulin overdose
Sepsis
Severe uremia (end-stage renal disease)
Toxins
Lead
Organophosphates
Ethylene glycol
Nutritional
Thiamine deficiency (terminal stage)
EPILEPSY
Functional
Idiopathic
Genetic
Structural
Postencephalitic
Posttraumatic
Postischemic (FIE, hypoxic event)

behavior.[5,14] Routine complete blood cell counts and serum chemistries in addition to preprandial and postprandial bile acids, resting ammonia levels, abdominal ultrasound, rectal portal scintigraphy and intraoperative portography, and liver biopsy are useful diagnostic aids. Low-protein diets, oral and parenteral antibiotics, antifibrotic agents, and lactulose are indicated for medical treatment of HE depending on the underlying cause.

Surgical correction is the treatment of choice for an extrahepatic shunt in the feline patient.[14] Placement of an ameroid ring constrictor on single extrahepatic portosystemic shunts in cats resulted in a low rate of surgical complication and postoperative mortality.[15] Many cats did have postoperative complications. Neurological complications included central blindness, hyperthermia, frantic behavior, and generalized motor seizures. The pathophysiological mechanism of postligational seizures is poorly understood.[14] Alterations in benzodiazepine concentration have been associated with post-ligational seizures. Animals may decompensate as a consequence of down-regulation of receptors and rapid decrease in concentration of circulating neurotransmitters.

Hypoglycemia

Hypoglycemia in adult cats is caused by insulin overdose, liver failure, sepsis, and rarely, insulin-secreting tumors.[5] The initial signs of hypoglycemia reflect the body's response to decrease of blood glucose rather than the hypoglycemia itself. Increase in sympathetic tone (release of norepinephrine and epinephrine) leads to adrenergic signs of tachycardia, dilated pupils, tremors, irritability, and vocalization (see Chapter 20). Because the brain relies on passive diffusion of glucose, and it is deprived of its energy substrates, signs progress rostral to caudal.[14] The cerebrocortical neurons are more susceptible to the effects of hypoglycemia. Initial forebrain signs of neuroglycopenia include confusion, dullness, and seizures. Caudal fossa signs and death ensue if the condition persists and goes untreated. Routine diagnostic testing and history usually differentiate between insulin overdose, sepsis, and liver disease.

Treatment with intravenous dextrose supplementation and elucidation of underlying cause of the hypoglycemia are key to management of the hypoglycemic patient. Prolonged hypoglycemia causing neuronal death may lead to a permanent seizure focus, and antiepileptic drugs are indicated if seizures persist after correction of the hypoglycemia.[5,14]

Hyperthyroidism

Hyperthyroidism is diagnosed in cats usually older than 6 years of age and can affect the central nervous system (CNS) and peripheral nervous system (PNS). Normally, the brain maintains thyroxine (T_4) and triiodothyronine (T_3) concentrations within a narrow range. The role of hyperthyroidism as a cause for seizures may be linked to the ability of thyroid hormones to decrease the electrical threshold of cerebral tissue directly. Other proposed mechanisms include changes in cerebral oxygen and glucose utilization, altered cerebral blood flow, and altered concentrations of neurotransmitters.[5,14,17] Systemic effects of hyperthyroidism have been discussed elsewhere. CNS signs include restlessness, irritability, aggression, hyperexcitability, aimless wandering, pacing, circling, abnormal sleep/wake patterns, generalized or partial motor seizures, and acute focal neurological deficits (similar to cerebrovascular accidents).[5,17] Diagnosis of hyperthyroidism is based upon elevated T_4 concentrations and nuclear scintigraphy (see Chapter 21). Treatment includes medications that decrease the production of thyroid hormone, radioactive iodine therapy, and surgical excision of the adenomatous thyroid tissue (see Chapter 22). Persistent seizure foci may be a sequela to hyperthyroidism, and the affected cat may require antiepileptic drug therapy after primary treatment for hyperthyroidism.

Hypertension

Normal systolic blood pressure in cats should measure less than 160 mm Hg. Common causes of hypertension in cats are hyperthyroidism, hypertrophic cardiomyopathy, and renal disease. Hypertensive animals usually present with retinopathy and blindness, but similar changes in the brain can lead to focal hemorrhage and atherosclerotic changes.[5,14] Almost half of the cats in one study had other neurological signs in addition to blindness.[18] Seizures, ataxia, nystagmus, sudden collapse, and paraparesis have been reported.[5,14] Diagnosis is based upon documentation of repeatable hypertension and elucidation of the underlying cause of the elevation. Therapy is aimed at reversing the hypertension using oral antihypertensive drugs and treating the underlying cause. Certain antihypertensive drugs (nitroglycerin) can cause cerebral vasodilation, which can worsen the encephalopathy. Permanent seizure foci may be a sequela to the effects of hypertension, and long-term use of antiepileptic drugs may be necessary.

Electrolyte Imbalances

HYPERNATREMIA/HYPONATREMIA. Sodium is the major extracellular osmol. Imbalances can lead to formation of osmotic gradients, which can have profound CNS and PNS effects. Clinical signs of hyponatremia are associated with the degree of the hyponatremia and the rapidity of onset. Clinical signs occur with sodium concentrations below 120 mEq/L. Cerebral edema occurs as a result of osmotic differences between the brain and the extracellular fluid. With chronicity (Na^+ <110 mEq/L), energy metabolism and transport mechanisms may be affected. Neurological signs initially include lethargy and vomiting that can progress to seizures, coma, and death. Rapid correction of chronic hyponatremia may lead to myelinolysis (not described in cats) in the thalamus and pons, a sequela of osmotic shifts and blood-brain barrier disruption.

Hypernatremia can occur as a result of free water loss from the body (adipsia). Clinical signs associated with hypernatremia manifest when the sodium concentration is above 170 mEq/L, which causes an increase in serum osmolality. Ataxia, tremors, myoclonus, tonic spasms, coma, and death can occur. Therapy for hypernatremia and hyponatremia is aimed at correcting the underlying cause in addition to correcting the sodium imbalance as described in the literature.[5,14]

Thiamine Deficiency

Thiamine is an essential, water-soluble B vitamin (B_1) that is a co-factor in the decarboxylation of pyruvate and α-ketoglutarate, and is a necessary co-factor for several steps of the Krebs cycle. Thiamine deficiency interferes with normal energy metabolism in the brain, and a buildup of lactic acid

ensues as the brain is forced into anaerobic metabolism.[5,14] Some fish (tuna and salmon) contain the enzyme thiaminase; if raw fish is prepared at home, cats may develop this deficiency. Central vestibular dysfunction is a classic neurological sign of thiamine deficiency. Generalized seizures usually occur in the terminal stages.[2,5] Diagnosis is based upon history, clinical signs, and response to treatment. Treatment entails thiamine supplementation (either injectable or oral) and supportive care.

Toxic Encephalopathies

LEAD TOXICITY. Common sources of lead include lead-based paint, cages, batteries, grease, and fishing sinkers. Cats are exposed to lead paint chips during home remodeling and ingest the lead through their grooming habits. Chronic exposure to small amounts of lead results in a toxicosis. The effect of lead on the nervous system occurs secondary to decreased blood supply because of capillary and small arteriolar damage. Laminar cortical necrosis is a common histological finding. CNS signs can include altered levels of consciousness, hyperexcitability, excessive vocalization, seizures (either partial or generalized), opisthotonus, paraparesis/plegia, muscle spasms, hyperesthesia, mydriasis, or blindness. Diagnosis is based upon history, clinical signs, and the finding of blood lead levels above 0.35 ppm. Treatment includes removal of lead from the gastrointestinal tract and use of lead chelators such as calcium EDTA.[5]

ORGANOPHOSPHATES AND CARBAMATES. Organophosphates (OP) and the carbamates are acetylcholinesterase inhibitors and common ingredients in flea shampoos and parasite dips. Accumulation of acetylcholine occurs at nerve endings, which results in overstimulation of cholinergic receptors of the somatic, autonomic, and central nervous systems.[5] Clinical signs reflect actions of acetylcholine on muscarinic and nicotinic cholinergic receptors. These signs include vomiting, ptyalism, lacrimation, diarrhea, and, on occasion, hyperactivity and seizure activity. Diagnosis is based upon the history of ingestion and clinical signs. Treatment consists of parasympatholytic agents, supportive care, and antiepileptic drug therapy. Atropine counteracts the muscarinic effects of OP or carbamate toxicity. Pralidoxime chloride (2-PAM, Protopam Chloride, Wyeth-Ayerst) is administered as soon as possible after exposure. 2-PAM disrupts the bond between the OP and acetylcholinesterase to form a complex that is eliminated in the urine. 2-PAM is most effective if administered within the first several hours after exposure before the OP "age" with time. Diphenhydramine is recommended to counteract the nicotinic effects of OP toxicity. More in-depth discussion for treatment is covered in the fourth volume of *Consultations in Feline Internal Medicine,* Chapter 48.

Hypoxia

Transient cerebral hypoxia is much more likely to cause seizures and syncope with seizure-like manifestations in cats than dogs.[9] These events can be precipitated by stress and exercise. Hypoxia often is a sequela of cardiovascular disease, hematological disorders, endocrinopathies, and ischemic events. Diagnosis and treatment are aimed at correcting the primary cause and controlling seizure events with antiepileptic drug therapy if activity persists.

Intracranial Etiologies

Intracranial causes of seizures are divided into structural and functional (idiopathic epilepsy). The literature suggests that structural brain disease is more common in cats than idiopathic epilepsy.[1-9] Structural brain disease in cats used to imply a more guarded prognosis. More recent studies indicate that some of these structural lesions may be nonprogressive, thus having a better prognosis.[3,9] The list of intracranial diseases causing seizures in cats is extensive (see Table 55-1). Selected diseases are highlighted in this chapter.

Neoplasia

Meningioma is the most common CNS neoplasm in cats. Meningiomas are characterized as slow-growing, space-occupying masses that are histopathologically benign in most cases. Masses can occur singly or in a multifocal pattern. Signalment includes cats older than 8 years of age. Male cats are more predisposed than female cats.* Clinical signs vary with lesion location, the forebrain affected most commonly. Clinical signs usually are progressive and lateralizing with a high incidence of focal or partial seizures. Other neurological signs observed are circling (usually toward the side of the lesion), behavior changes, contralateral visual loss, partial cranial nerve deficits, conscious proprioceptive loss, and hemiparesis. Diagnosis and treatment options are discussed in more detail in the fourth volume of *Consultations in Feline Internal Medicine,* Chapter 50.

Primary and secondary CNS lymphoma also can cause seizure activity.[3,5,19-21] The signalment of cats with LSA tends to be young to middle-age (between 7 and 10 years). No sex predilection exists. The forebrain is a common site and presenting clinical signs are similar to those of meningiomas. Other intracranial neoplasms include glial tumors (astrocytomas, oligodendrogliomas), pituitary tumors (adenomas/adenocarcinomas), choroid plexus tumor, medulloblastoma, and gangliocytoma. Metastatic tumors include renal lymphoma and mammary adenocarcinoma.[16,19] (See Chapter 54 for a complete discussion of intracranial tumors.)

Inflammatory Infectious Diseases

Infectious diseases such as feline infectious peritonitis (FIP), feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), and toxoplasmosis are reported as structural causes of seizures in cats.† The multifocal lesion distribution of these diseases may cause focal, partial, or generalized seizures. The incidence of seizures is reported variably in the literature, and seizure activity often is accompanied by concurrent systemic illness (FIP and toxoplasmosis).[22]

According to some reports, the most common structural cause of seizures in cats (47 per cent) is a nonsuppurative meningoencephalitis of an unknown etiology, but suspected to be viral or immune-mediated.[2,8,9] Recurrent seizures were the only clinical sign in the majority of cats in this study and appeared to be self-limiting, but seizures persisted in some cats. It is believed currently that these cases are likely to be the result

*References 3,5-7,16,19,20.
†References 2,3,5,6,8,9,16,22-24.

of a non-FIP virus yet to be identified.[8] Cats of all ages were affected and demonstrated the full spectrum of seizure activity from focal events up to status epilepticus.[9] Results of neurodiagnostic testing were within normal limits. Most cats had an excellent outcome on anticonvulsants, including those with severe and initially refractory seizures. In another study describing nonsuppurative meningoencephalitis, it was the third most frequent diagnosis after neoplasia and FIP as a cause of seizures in cats. In these cases, concurrent systemic illness and mild to moderate changes in cerebrospinal fluid were observed.[12] Symptomatic treatment includes antiepileptic drug therapy and antiinflammatory drugs if other infectious/inflammatory diseases have been excluded.

OTHER INFECTIOUS INFLAMMATORY CNS DISEASES. Besides CNS viral infections, other infectious agents are considered relatively rare in cats and are associated less commonly with seizures as the only clinical abnormality. Often these diseases are rapidly progressive and accompanied by disseminated systemic illness and abnormal neurodiagnostic results.[25] Disease examples include bacterial meningitis/meningoencephalitis, brain abscessation, and subdural empyema.[5,8,9,16] Cryptococcosis is the most common systemic mycosis in cats and has been associated with CNS involvement and seizure development. Cryptococcosis has a predilection for the nasal cavity, and involvement of the cribriform plate and prefrontal lobe is not uncommon.

Vascular Disease

CNS vascular diseases in cats are primary or secondary.[5,13,14,18] Cats with seizures secondary to vascular disease often present with signs of a peracute to acute onset of lateralizing or diffuse forebrain deficits, variable degrees of tetraparesis or paraparesis, and ataxia that improves over a period of days to months. In some instances, clinical signs often improve but then plateau with residual neurological deficits.

Feline Ischemic Encephalopathy

Feline ischemic encephalopathy (FIE) has been described as a cerebral infarction syndrome characterized by a peracute onset of nonprogressive, asymmetrical signs of forebrain dysfunction. Behavior changes and contralateral deficits often are described. Acute onset of cluster seizures or aggression can be the first and predominant clinical signs. Clinical signs improve over weeks to months; behavioral abnormalities may persist. A definitive cause still remains an enigma. Thrombosis or vasospasm of the middle cerebral artery subsequently leads to cerebral ischemia.* Cardiomyopathy-associated thrombosis, FIP-induced vasculitis, aberrant nematode migration, and cerebral *Cuterebra* infection have been proposed as mechanisms. FIE was considered the second most common cause of seizures in cats.[2,9] CSF analysis is characterized by mild elevation in protein concentration with minimal evidence of inflammation. MRI reveals mild to marked asymmetry of the cerebral hemispheres and hydrocephalus ex-vacuo caused by replacement of CSF in areas with parenchymal atrophy.[2]

*References 2,3,5,6,9,12.

Polycythemia

The pathophysiology of polycythemia is related to an increase in erythrocytes causing an increase in blood viscosity. Secondary consequences are impaired blood flow, blood stasis, and tissue hypoxia. Neurological sequelae include seizures (focal, partial, or generalized), behavior changes, and ptyalism. Other systemic signs are polyuria/polydipsia, lethargy, and muscle twitching. Diagnosis is based on determining the underlying cause. Treatment addresses the underlying cause, and palliative antiepileptic drug (AED) therapy is recommended.[2,5]

Trauma

Vehicular accidents, height-related falls, and blunt trauma can cause severe brain injury in cats if they survive the primary impact (Figure 55-4). Clinical signs are dependent upon neuroanatomical location and lesion severity. Neurological dysfunction includes seizures, diffuse or lateralizing forebrain deficits, hemiparesis or tetraparesis, and ataxia. Brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) can assess lesion extent and establish options for surgical management. Rapid and aggressive supportive care is essential to outcome for the head trauma patient. Assessment of the whole patient is important, because injuries to multiple systems are not uncommon. Medical management for head trauma consists of providing a functional airway and promoting vascular support with appropriate fluid therapy. Adjunctive therapies consist of osmotherapies with mannitol and/or hypertonic saline, hyperoxygenation, and meticulous patient monitoring. Surgical intervention is recommended for the patient with deteriorating neurological status that is refractory to medical therapies. Clinical signs may improve, but residual neurological deficits are common.[3,5,26]

Malformations and Degenerative Disorders

Hydrocephalus and other primary brain anomalies often have clinical manifestations of seizures. Degenerative disorders such as the lysosomal storage diseases affect cats less than 1 year of

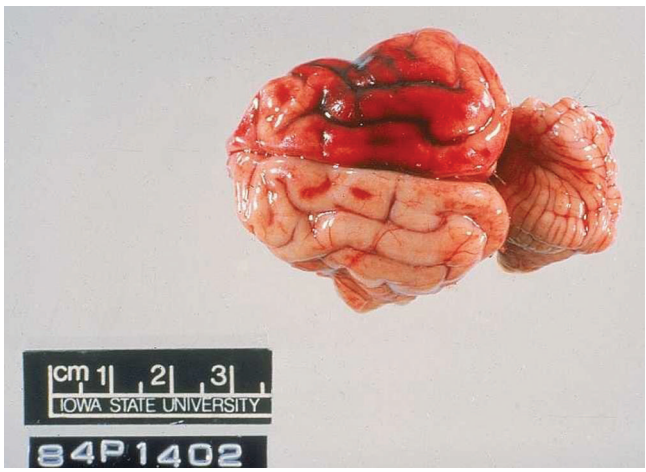

Figure 55-4. Postmortem example of intraparenchymal hemorrhage and cerebral contusions in a cat that sustained severe head trauma as a cause of seizures.

age and are slowly progressive. Seizures usually develop late in the disease course after onset of other neurological deficits and systemic effects.[6,9]

Primary or Idiopathic Epilepsy

A significant percentage of cats have seizures of an undetermined etiology. An underlying cause is suspected but never proven antemortem with routine neurodiagnostic testing. Differential diagnoses include posttrauma, postencephalitis, and postischemic events. The neurological examination is normal in the interictal period, and clinical signs are considered quiescent and nonprogressive. This form of epilepsy probably is more common than pure idiopathic epilepsy in cats. Diagnostic imaging using MRI may reveal evidence of previous trauma. Histopathological studes have shown gliotic scars in cats with previous encephalitis. The incidence of idiopathic epilepsy in cats ranges between 0 per cent and 60 per cent.[2,9] Idiopathic epilepsy is suspected when other pathological causes have been excluded.[2,5,6,9]

DIAGNOSTIC APPROACH

Thorough patient evaluation is essential for determining whether other abnormalities could contribute to the underlying seizure episode. A complete history is a vital component of the patient assessment. The clinician should be aware of the onset of clinical signs, progression, vaccination status, travel history, environment (indoor versus outdoor), drug history, and nutritional status. The seizure episodes are defined thoroughly to determine actual occurrence of a seizure or mimicking clinical signs. Cardiovascular-related syncope, vestibular dysfunction, behavior disturbances, or pain are examples that can mimic a seizure event. Physical examination is important for detecting systemic disorders that may manifest neurological signs secondarily. The neurological examination will determine the presence of neurological dysfunction. The neuroanatomical localization for seizures is the forebrain. The neurological examination also may define the localization as focal, multifocal, or diffuse (Table 55-2). A minimum database for a cat with seizures should include a complete blood count, serum biochemistry profile, urinalysis, preprandial and postprandial bile acids, retinal fundic examination, and tests for FeLV and FIV. Cats older than 5 years of age also should have blood pressure monitoring, thyroid hormone (T_4) screening, thoracic and abdominal radiographs, and cardiac evaluation (ECG and echocardiography). Cats with suspected intracranial disease need further neurodiagnostic testing to evaluate for a possible structural lesion.[1-9,14,20]

Table 55-2 | **Diagnostic Evaluation of Feline Seizures**

History
Previous illness/trauma
Environment (indoor/outdoor/cattery)
Previous therapies
Age at onset of seizures/progression
Type and frequency of seizures
Interictal signs
Nutrition
Physical examination
Neurological examination
Fundic examination
Hematological assessment
CBC/serum chemistry/urinalysis/serum T_4
Bile acids/blood ammonia
FeLV/FIV blood tests
Toxoplasmosis/cryptococcosis serum titers
FIP PCR on blood/CSF
Special chemistries (lead, cholinesterase)
Other diagnostics
Radiography (thoracic/abdominal radiographs/echocardiogram/abdominal ultrasound/thyroid scan/portogram)
ECG/blood pressure
Neurodiagnostics
CT scan
MRI
CSF analysis (cell count/cytology/total protein)

Neurodiagnostic Testing

Ancillary neurodiagnostic testing frequently includes brain imaging (CT or MRI) and CSF analysis. MRI is more sensitive than CT in detection of parenchymal lesions and determining lesion extent.[19] Imaging should be performed before CSF collection. Cisternal puncture would be detrimental in cases of increase in intracranial pressure. Potential risks for herniation have been associated with intracranial neoplasia and inflammatory disease.[2] Abnormalities on CSF analysis indicate presence of a structural brain lesion. These abnormalities can be nonspecific and a definitive diagnosis is made rarely based upon results of CSF analysis alone.[2,5,9,25] Serology performed on CSF for infectious agents such as FIP-inducing coronavirus, *Cryptococcus neoformans*, and *Toxoplasma gondii* may prove more sensitive than similar tests on serum. The main objective for diagnostic testing is to determine viable options for disease-specific medical or surgical treatments, in addition to possible antiepileptic drug therapy.

MEDICAL MANAGEMENT OF SEIZURES

General Principles

AED therapy is initiated if seizures occur more frequently than once a month, if the patient begins to have an acute onset of cluster seizures or status epilepticus, or when the owner has a strong desire to treat the seizures regardless of frequency. AED therapy usually is warranted when seizures are caused by structural lesions of the brain. Long-term maintenance therapy often is indicated with persistent seizure activity.[1-9,27] Realistic goals of AED therapy are to decrease the frequency of the seizures, reduce their severity, and enhance the quality of life for the patient and pet owner. The prognosis should not be based upon the severity of the seizure. Some cats who present with status epilepticus may respond extremely well to anticonvulsant therapy. In my experience, early aggressive therapy is the key to seizure control in acute and chronic situations. Patients refractory to medication need reevaluation for progression of the intracranial disease not addressed previously, assessment of owner compliance, and additional monitoring for drug tolerance. Many owners may have difficulty administering oral medications to their cats and need to be educated about consistency of drug administration and routine drug monitoring. Journal documentation of seizure activity is a useful tool for assessment of medication compliance.

Maintenance Therapy

Phenobarbital

Phenobarbital is the AED therapy of choice for control of seizures in cats. Pharmacokinetics have been well established and most veterinary laboratories perform routine drug monitoring. Phenobarbital is relatively safe and inexpensive and has proven efficacy for seizure control in cats. The recommended dose is 1.25 to 2.5 mg/kg PO q12h. The elimination half-life in cats can range between 43 and 76 hours. Steady-state serum concentration is achieved within 9 to 16 days of starting therapy. Serum drug concentrations ideally should be measured within 2 to 3 weeks of initiating therapy or after a change in dosage. Therapeutic blood levels are similar to those reported in dogs (25 to 40 µg/ml). Optimal recommended therapeutic target range for serum phenobarbital concentrations for cats is between 23 and 30 µg/ml. This target range maximizes seizure control with fewer side effects.[1-9,24,27-29] The pharmacokinetics of phenobarbital in cats are less predictable than in dogs. Phenobarbital is metabolized primarily by the liver. Establishing a baseline of liver function using pre- and post-bile acid testing is recommended before initiating maintenance phenobarbital doses.[6] Serum concentrations should be evaluated every 6 months.[2,7,8] Periodic monitoring of the complete blood count, serum biochemistry profile, and bile acids is recommended. Side effects of phenobarbital include sedation, ataxia, polyphagia, and weight gain. Sedation and ataxia usually are transient and subside within 1 to 2 weeks after initial administration or a change in dose, although exceptions do occur.[6] Cats are considered sensitive to the sedative effects of AEDs, related to a slower elimination rate. The dose should start low and increase incrementally. In my experience, drug-associated polyuria, polydipsia, and polyphagia occur less commonly in cats than in dogs. Rare idiosyncratic reactions include blood dyscrasias (thrombocytopenia, leukopenia), hepatotoxicity, dermatitis, and persistent, unusual behavioral disturbances.[6,24]

Benzodiazepines

Oral diazepam administration has been advocated as a maintenance or adjunctive therapy for seizure control in cats.* In contrast to dogs, diazepam is metabolized in cats more slowly with a half-life that ranges between 15 and 20 hours. Diazepam can be administered every 8 to 12 hours. A recommended dose is 0.5 to 1.0 mg/kg/day PO divided q8-12h. In some cases, the dose can be increased to 2.0 mg/kg and is tolerated safely. Development of drug tolerance is rare in cats, and only a 20 per cent rate of drug resistance has been reported.[3,6] Common side effects include sedation and an increase in appetite. Fulminant hepatic failure associated with oral administration of diazepam has been reported as an idiosyncratic drug reaction and has limited its use as a primary AED.[30] Acute hepatic necrosis can occur as early as 5 days after initiation of the recommended oral dose.[5,6,29] Although fairly uncommon, this side effect frequently is fatal. Liver enzymes and bile acids should be monitored 5 to 7 days after initiation of therapy and every 6 months thereafter.[6]

*References 1-3,5-7,9,24.

Potassium Bromide

Potassium bromide has gained popularity as an adjunctive AED therapy in cats with seizures when phenobarbital alone is ineffective for adequate seizure control.[6-8,27,31,32] Bromide is absorbed in the proximal small intestine and is eliminated through the kidneys. The half-life has been reported to be 13 days in cats, roughly one third the time of that reported in dogs. The steady-state usually is attained within 2 months. Minimum therapeutic concentrations are reached within 3 weeks of initiating therapy. The recommended dose of bromide in cats is 20 to 30 mg/kg PO q24h.[31,32] The target range for serum bromide concentration is between 1.0 and 1.6 mg/ml.[32] Adverse side effects occur in approximately 50 per cent of cats administered bromide. Side effects include polydipsia, vomiting, weight gain, sedation, and coughing. Coughing has a reported incidence in 35 to 42 per cent of cats.[6,8,31-33] A study at Ohio State University reported 11 of 26 cats treated with bromide developed a persistent, nonproductive cough.[33] Coughing is acute in onset and may be associated with dyspnea. Thoracic radiographs reveal mild to marked peribronchial infiltrates, similar to those observed with asthma. Bronchoalveolar lavage has revealed inflammatory changes with eosinophils dominating.[8,33] Withdrawal of the drug often results in resolution of clinical signs; however, three of 17 cats reportedly died from complications associated with drug administration. A thorough history of prior airway disease must be obtained before initiation of bromide therapy. The drug should be discontinued immediately if coughing is reported by the owner.[6]

Adequate and Inadequate Seizure Control

Adequate control of seizures in cats can be monitored by pet owners recording seizure events. Successful management is defined as decrease in seizure severity and frequency and a good quality of life. In my experience, three to four seizures a year is considered acceptable. If seizure severity and frequency are not improved after 3 to 4 weeks of therapy, recommendations include reevaluating the underlying cause and monitoring drug concentrations. If the serum drug concentrations are below or at the low end of the therapeutic range, the dosage is increased incrementally. If drug concentrations are well within the therapeutic range, or if the serum level does not rise with an increase in drug administration (tolerance), adjunctive therapy may be pursued. Options to discontinue AED therapy may be considered when seizure activity ceases for 6 to 12 months.[7] The standard recommendation is to decrease the dose by one third every 2 weeks. In my opinion, if the cat is tolerating the drug and showing minimal side effects, I would not discontinue the medication.

Cluster Seizures and Status Epilepticus

The treatment of status epilepticus in cats is similar to that in dogs.[1-9,27] Intravenous or per rectal diazepam administration at a dose of 0.5 to 1.0 mg/kg often provides cessation of seizure activity. Diazepam alone usually is effective because of its longer half-life. If multiple bolus administration is ineffective, a continuous rate infusion (CRI) of diazepam at 0.5 mg/kg/hr is considered, taking care to protect it from light. I recommend administration of the CRI for up to 2 hours and reassessment of seizure control. Some authors recommend administration of

Table 55-3 | **Summary of Antiepileptic Drug Therapy in Cats**

DRUG	INDICATIONS	ADMINISTRATION	MONITORING	POTENTIAL ADVERSE EFFECTS
Phenobarbital	Identification of a structural lesion Status epilepticus Two or more isolated seizures within a 6-week period The first observed seizure is within a week of head trauma Prolonged, severe, or unusual postictal periods	Initial oral doses 2.5-5 mg/kg PO daily (once or divided q12h) IV loading dose: Total mg IV = (Body weight [kg] × (0.9 L/kg) × (15 µg/ml)	Measure trough serum phenobarbital Therapeutic range is 10-30 µg/mL Evaluate serum chemistry panel at 45 days and every 6 months	Transient: lethargy, behavior change Persistent: polyuria, polydipsia, polyphagia, weight gain, excessive sedation Severe: hepatotoxicity
Potassium bromide	Persistent seizure activity with steady state trough serum phenobarbital concentration > 20 µg/mL for at least 1 month Hepatotoxicity from phenobarbital or primary hepatic disease Severe cluster seizures Poor toleration of adverse effects of phenobarbital	Potassium bromide in capsule formulation at 100 mg per capsule Dose: 20-30 mg/kg/day PO with food as initial dose	Measure trough serum concentrations at 21 days, 90 days and every 6 months after initiation Therapeutic range: 100-200 mg/dL (1.0-2.0 mg/mL) with concurrent phenobarbital: >200 mg/dL (2.0 mg/mL) as sole therapy	Lethargy Polydipsia Polyuria Pancreatitis Ataxia Stupor Cough
Diazepam	IV: Generalized cluster epileptic seizures Status epilepticus PO: Maintenance treatment as for phenobarbital therapy	0.5 mg/kg IV 0.5 to 2.0 mg/kg PO q12h or q8h	Plasma nordiazepam concentration can be measured, but rapid elimination half-life makes interpretation difficult Liver enzyme changes should be monitored at 7, 15, 45 days after start and every 6 months to evaluate for hepatotoxicity	Lethargy and sedation Polydipsia Polyuria Polyphagia Weight gain Idiosyncratic hepatotoxicity
Clorazepate	Maintenance treatment as for phenobarbital therapy	3.75 to 7.5 mg PO q6-8h	As for diazepam	As for diazepam

From Podell M: Antiepileptic drug therapy. Clin Tech Small Anim Pract 13:185, 1998.

the CRI for a minimum of 6 hours.[2,9] A bolus administration or CRI (0.5 to 1.0 mg/kg/hr) of phenobarbitol also can be administered. Propofol also has AED properties. A propofol CRI (0.1 to 0.4 mg/kg/min) can be used short-term in cats. Heinz body production occurs in cats with repeated use of propofol. Heinz bodies are produced as a result of oxidative injury to RBCs. Bolus and CRI administration has potential for severe respiratory depression. Intratracheal intubation and additional ventilatory support may be necessary. Cats may be profoundly sedated after parenteral treatment with AEDs.[9] Monitoring vital indices serially until the cat is acclimated to the AED is important. Additional supportive care includes fluid therapy, temperature regulation, oxygen supplementation, continuous electrocardiogram, and frequent turning. Blood glucose, electrolytes, and urine output are assessed frequently. Choice of a maintenance AED is considered while providing initial seizure control. See Table 55-3 for a summary of AED therapy in cats.

PROGNOSIS

An underlying structural lesion often is the cause for seizures in cats. Prognosis for seizure control is dependent upon the type of structural lesion. The treatment of the acquired cause should be addressed first. No correlation exists between the severity of the seizures and outcome.[2,9,6,24] Side effects and adverse reactions may limit use of some AEDs. In cats with no detectable structural lesion but in which an acquired cause is still suspected, early and appropriate AED management can result in adequate long-term seizure control.

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Chapter 56

VESTIBULAR DISORDERS

Simon R. Platt

Cats have the ability to control posture and movements of the body and eyes relative to their external environment. The vestibular system mediates these activities through a network of receptors and neural elements. This system integrates peripheral sensory information from vestibular, somatosensory, and visual receptors, in addition to motor information from the cerebellum and cerebral cortex. Central processing of these inputs occurs rapidly and provides coordinated relevant muscle movements. Although the vestibular system is considered as a special sense, most vestibular activity is conducted at a subconscious level. Disease leading to dysfunction of the vestibular system can lead to dramatic signs of dysequilibrium. Treatment and prognosis for causes of dysequilibrium differ, depending on whether the peripheral or central components of the system are affected. This chapter outlines relevant anatomy of the vestibular system with emphasis on the clinical signs of vestibular dysfunction. Additionally, an overview of the diseases responsible for vestibular dysfunction in cats is provided.

NEUROANATOMY OF THE VESTIBULAR SYSTEM

The vestibular system can be divided into peripheral components located in the inner ear, and central nervous system (CNS) components. Three major CNS areas receive projections from the peripheral sensory receptors of the vestibular system: the cerebral cortex, the spinal cord, and the cerebellum. Projection pathways to the cerebral cortex incorporate extensions to the extraocular muscles.

Projection Pathways to the Cerebral Cortex and Cranial Nerve Nuclei

Three neurons make up the pathway responsible for the sensory input of head and body position and movement to the cerebral cortex (Figure 56-1).

Neuron 1

The location for the first-order neuron is within the vestibular ganglion of cranial nerve VIII or the vestibulocochlear nerve. The axon projects to the ipsilateral vestibular nuclei. These neurons receive input from the vestibular receptors contained within the membranous labyrinth that is surrounded by a bony labyrinth located in the petrous temporal bone. The membranous labyrinth consists of four fluid-filled, communicating compartments; these include the saccule and utriculus, three semicircular ducts, and a cochlear duct (Figure 56-2).[1-4] Specifically, the vestibular portion of the eighth cranial nerve innervates five sites: the crista of the ampulla of each of the three semicircular ducts and the maculae of the utricle and saccule. Each semicircular duct is orientated at right angles to the others and connects at both ends with the utriculus, which in turn communicates with the saccule. Movement of endolymph contained within the membranous labyrinth is responsible for stimulation of the receptors; the endolymph is thought to be derived from blood.[5]

The crista detects head movement. Neuroepithelial cells are stimulated by the movement of the crista's gelatinous cupula secondary to the flow of endolymph as the head turns; any movement deflects the cupula and cilia, which leads to their depolarization and propagation of nerve impulses to the vestibular neurons. Primary function of the crista involves dynamic equilibrium with regard to acceleration and deceleration.[1-4,6,7]

The maculae detect head orientation; the macula of the utricle is parallel to the ground with its "hairs" pointing dorsally, and the macula of the saccule is vertical with its "hairs" pointing laterally. Constant input from gravity acts upon the neuroepithelial cells of each macula, subsequently causing them to fire. These slow-adapting receptors are responsible for sensing static position of the head and linear acceleration and deceleration.[2-4,6,7]

The sensory neurons of the vestibulocochlear nerve consist of cell bodies in the spiral ganglion located within the modiolus of the cochlea. The vestibulocochlear nerve and the facial nerve exit the petrous temporal bone through the internal

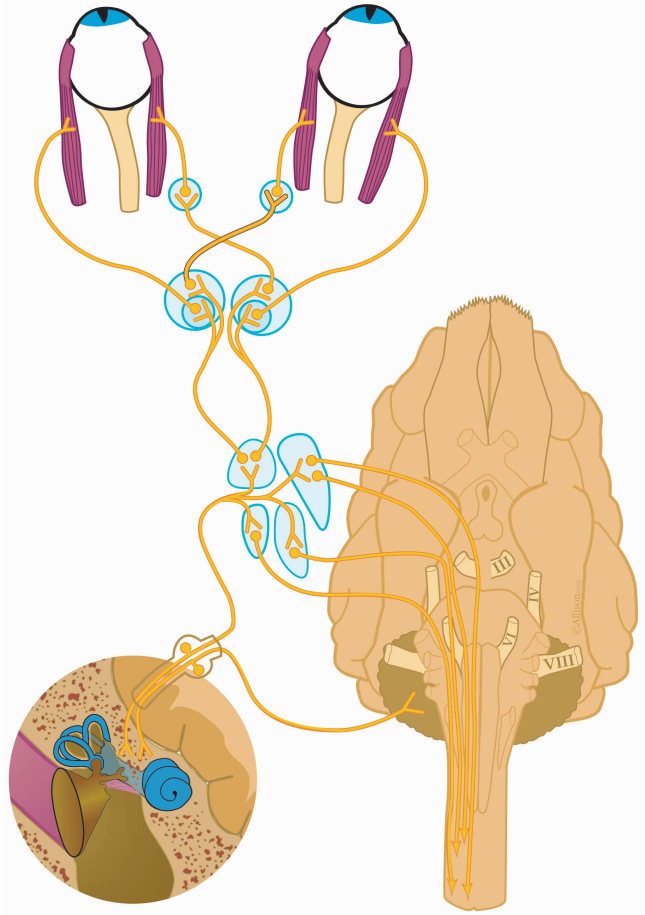


Figure 56-1. Schematic overview of the neuroanatomy of the vestibular system. (From Platt S, Olby N, editors: Manual of canine and feline neurology, ed 3, British Small Animal Veterinary Association, 2004.)

acoustic meatus. The nerve enters the medulla of the brainstem at the ventrolateral margin of the trapezoid body. A branch of the vestibulocochlear nerve enters the medulla directly, and a branch travels within the acoustic stria on the dorsal surface of the medulla and caudal cerebellar peduncle before entering the brainstem. The course of the vestibulocochlear nerve stays within the cranium.[1,3,5,7]

Neuron 2

The location of the cell bodies for the second-order neuron is the vestibular nuclei in the medulla oblongata. Four paired vestibular nuclei exist: the caudal vestibular nucleus located medial to the caudal cerebellar peduncle, the medial vestibular nucleus that lies medial to the caudal nucleus, the lateral vestibular nucleus positioned dorsal to the caudal nucleus, and the rostral vestibular nucleus (Figure 56-3). The lateral and the rostral nuclei are juxtapositioned dorsally to the cerebellar peduncles.[1,3,5,6]

Similar to the auditory pathway, axons from the vestibular nuclei have ipsilateral and contralateral projections. Some axons course within the medial longitudinal fasciculus and project to the contralateral medial geniculate nucleus of the thalamus. Ascending fibers within the fasciculus give off numerous branches to the motor nuclei of cranial nerves III, IV, and VI before synapsing in the medial geniculate nucleus. This pathway coordinates conjugate eye movements associated with changes in position of the head. The medial longitudinal fasciculus also contains fibers that descend to the spinal cord. Some axons have afferent projections from the vestibular nuclei to the vomiting center located within the reticular formation.[1,2,5,6]

Neuron 3

Cell bodies for the third-order neuron are located in the medial geniculate nucleus, within the medial geniculate body. These axons project to the cerebral cortex via the internal capsule and via a poorly defined pathway to the temporal lobe.[1,4,5]

Projection Pathways to the Spinal Cord

Two vestibulospinal pathways, termed lateral and medial vestibulospinal tracts, correspond with their origin from the vestibular nuclei. Fibers from the lateral vestibular nucleus descend ipsilaterally the entire length of the spinal cord in the ventral funiculus to synapse with alpha and gamma motor neurons of the extensor muscles.[1] This pathway is facilitatory to ipsilateral extensor muscles and inhibitory to ipsilateral flexor muscles and contralateral extensor muscles.

Fibers from the medial vestibular nucleus descend the spinal cord in the medial longitudinal fasciculus located in a dorsal area of the ventral funiculus. These fibers synapse in the cranial area of the thoracic spinal cord with cervical motoneurons that control head position and maintain equilibrium.

Projection Pathways to the Cerebellum

Projection pathways between the vestibular nuclei and the cerebellum course through the caudal cerebellar peduncle. Fibers from the vestibular nuclei synapse in the ipsilateral flocculonodular lobe (the flocculus of the hemisphere and the nodulus of the caudal vermis) and the fastigial nucleus of the cerebellum.[1] Fibers from the fastigial nucleus of the cerebellum synapse in the vestibular nuclei. Projections from the cerebellum have a strong influence over the activity of the vestibular nuclei.

CLINICAL SIGNS OF VESTIBULAR DYSFUNCTION

The vestibular system maintains equilibrium through ipsilateral tonic input to the muscles of the head, neck, and torso. An asymmetrical lesion causes loss of the ipsilateral extensor system and causes the extensor system on the contralateral side to become functionally "dominant." Clinical signs are recognized as ipsilateral hypotonicity and contralateral hypertonicity. Unilateral vestibular disease produces ipsilateral dysfunction.

Common clinical signs of vestibular disease are head tilt, nystagmus, and ataxia; these may be present as single entities or as a combination of signs (Figure 56-4). The primary aim of the neurological examination is to determine if these vestibular signs are due to a peripheral vestibular system (inner ear) disease or a central vestibular system (brainstem and/or cere-

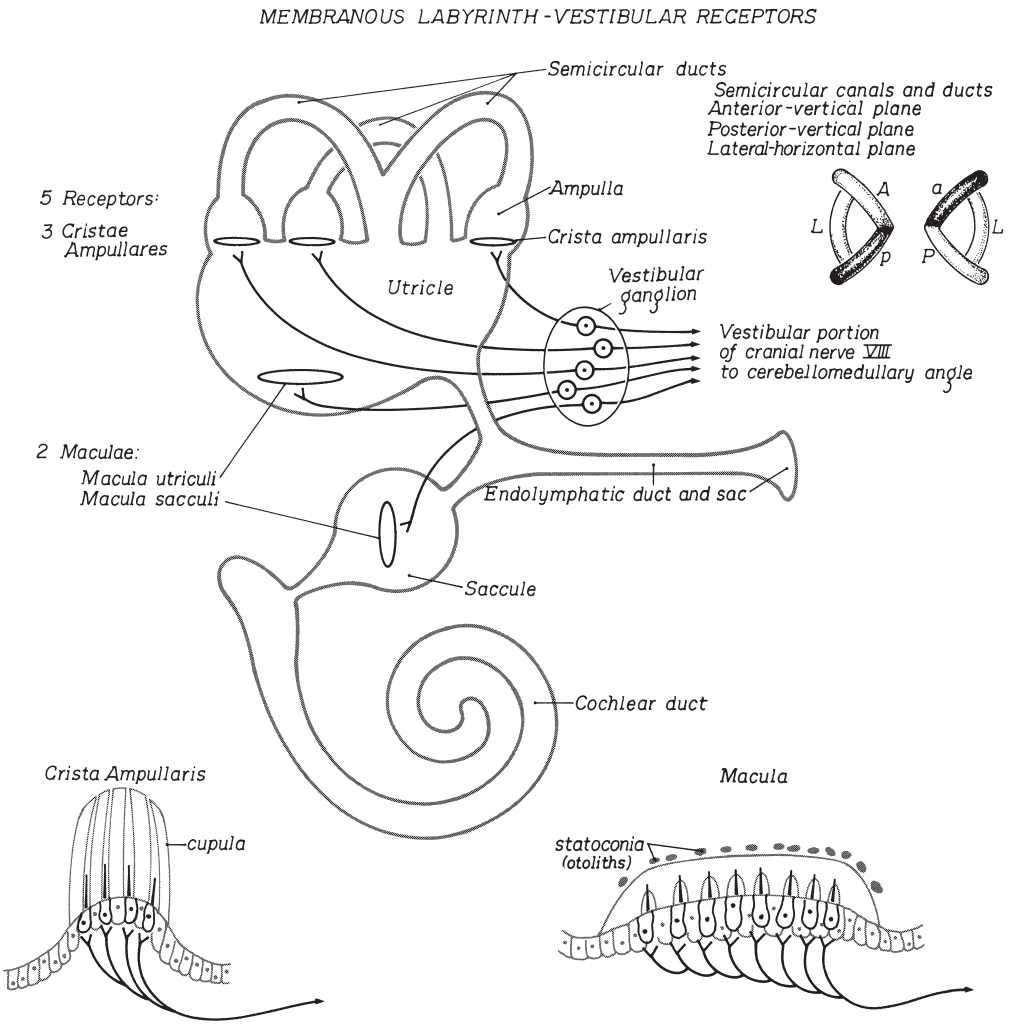


Figure 56-2. Illustration representing the structure and orientation of the semicircular ducts and the vestibular receptors. (From De Lahunta A, editor: Veterinary neuroanatomy and clinical neurology, ed 2, Philadelphia, 1983, WB Saunders.)

bellum) disease. Neuroanatomical localization determines the most appropriate diagnostic tests, the differential diagnoses, and the prognosis. Essential determination of whether these signs are due to a peripheral or central disease may be possible by the identification of associated neurological signs that are associated only with central disease.[1,3] Signs of central vestibular syndrome suggest brainstem involvement and are not present in patients with inner ear disease except in cases of direct extension of the disease process,[8] such as can be seen with otitis media/interna[9] and neoplasia.[8]

Clinical Signs Specific for Vestibular Dysfunction

Head Tilt

Loss of equilibrium most commonly is represented clinically as a head tilt (Figure 56-5 and Table 56-1). A head tilt may be present with either central or peripheral vestibular disease. The head tilt is always toward the side of the lesion with peripheral disease but may be to either side with central disease. A head tilt that is opposite to the side of the lesion is *paradoxical*. This can be seen with lesions of the flocculonodular lobe of the cerebellum or the supramedullary part of the caudal cerebellar peduncle, with sparing of the vestibular nuclei in the rostral medulla. The head tilt often is accompanied by ipsilateral cerebellar signs, paresis, and postural reaction deficits.[1,3,4,10] The mechanism by which the paradox of vestibular signs is contralateral to the lesion is not well understood. A loss of cerebellar inhibition over intact vestibular nuclei could result in hyperactivity of the latter, which simulates a relative loss of function on the other side.[1]

Cats with bilateral peripheral vestibular disease do not have asymmetrical lesions such as a head tilt, but have a characteristic "side-to-side" head movement (Figure 56-6).

Nystagmus

Pathological or spontaneous nystagmus is an involuntary rhythmic oscillation of both eyes, which can occur when the head is still or can be induced with a change in head position. This is a sign of altered vestibular input to neurons of cranial nerves that innervate the extraocular eye muscles.[10] This is in contrast to *physiological* nystagmus, which can be induced in normal cats by moving the head from side to side, best achieved by holding the cat in the air and moving the whole cat's body

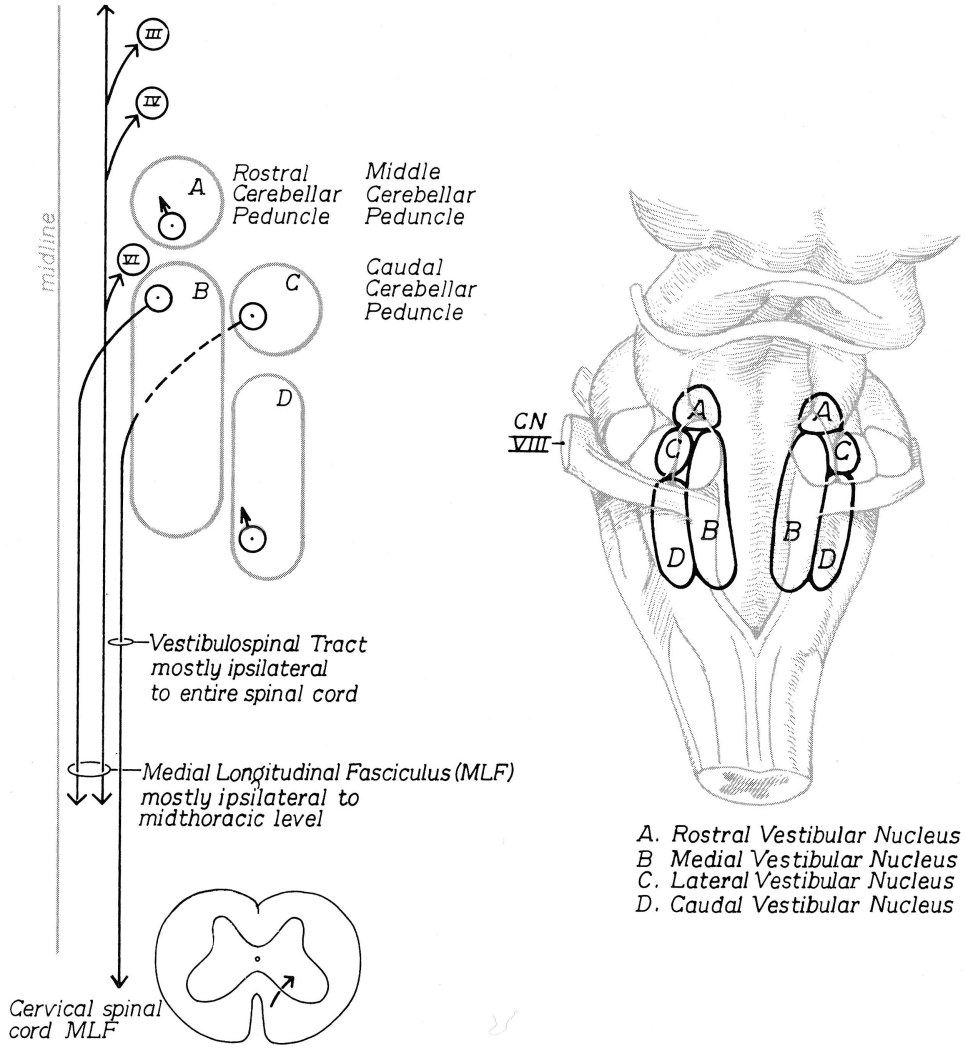


Figure 56-3. Schematic depiction of the vestibular nuclei, their location in the brainstem, and relationship to the long tracts of the central nervous system. (From De Lahunta A, editor: Veterinary neuroanatomy and clinical neurology, ed 2, Philadelphia, 1983, WB Saunders.)

Table 56-1 | **Neurological Examination Findings of Peripheral and Central Vestibular Dysfunction**

CLINICAL SIGNS	PERIPHERAL VESTIBULAR DISEASE	CENTRAL VESTIBULAR DISEASE
Head tilt	Toward the lesion	Toward the lesion or away from the lesion if paradoxical disease
Spontaneous nystagmus	Horizontal or rotatory with the fast phase away from the side of the lesion; rarely positional	Horizontal, rotatory, vertical, and/or positional with the fast phase toward or away from the lesion; direction of nystagmus can change with change in head position
Paresis/proprioceptive deficits	None	Common ipsilateral to the lesion
Mentation	Normal to disorientated	Depressed, stuporous, obtunded, or comatose
Cranial nerve deficits	Ipsilateral CN VII deficit	Unilateral or bilateral CN V, VII, IX, X, & XII ipsilateral deficits
Horner's syndrome	Common ipsilateral to lesion	Uncommon
Head tremors	None	Can occur with concurrent cerebellar dysfunction
Circling	Infrequent but can be seen toward side of lesion	Usually toward the side of the lesion

to each side (Figure 56-7). Physiological nystagmus allows the animal to maintain visual fixation on a stationary point and is called the vestibulo-ocular reflex (Figure 56-8).[8] The fast phase is toward the direction of the head movement and represents the corrective repositioning of the eye as the extraocular muscles reach their stretch threshold after the slow phase.[8] Delayed physiological nystagmus can be seen with peripheral or central vestibular disease.

Pathological nystagmus may be horizontal, rotatory, or vertical in direction (Figure 56-9). Vertical nystagmus implies a central vestibular lesion. If nystagmus of any direction is induced only when the head is placed in an unusual position, it is known as *positional* nystagmus (Figure 56-10), which may be more common with, but not specific for, central disease; this term also may refer to nystagmus that changes its predominant direction with altered head positions. A reliable way to induce

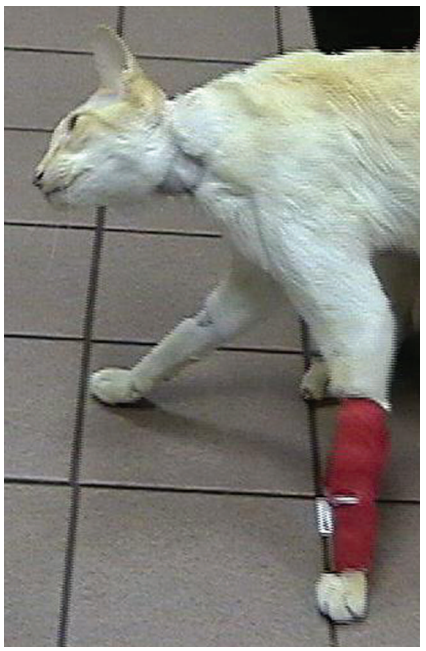


Figure 56-4. A 7-year-old Siamese with a right-sided head tilt demonstrates a profound wide-based stance.

Figure 56-5. A right-sided head tilt in a domestic long-haired cat.

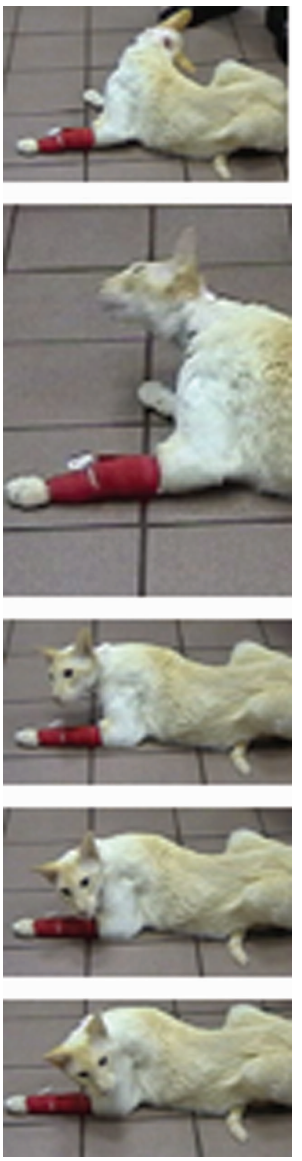


Figure 56-6. A 7-year-old Siamese with wide excursion of the head from right to left *(top to bottom),* resulting from bilateral vestibular disease.

positional nystagmus is to decompensate the cat by quickly positioning the cat on its back.

Eye movements typically are described to have a slow and fast phase. Damage to the vestibular system on one side impedes the resting baseline activity on this side, with the normal side continuing to emit baseline activity, now interpreted as head rotation to the normal side.[3,5,7,12] Therefore, the nystagmus occurs with the fast phase away from the damaged side and with the slow phase directed commonly toward the affected side; the exception is in the case of paradoxical disease (see section on head tilt above). The direction also can depend on whether the lesion is irritative or destructive to the vestibular system.[1] With acute onset nystagmus, the eyelids may be seen to contract at a rate corresponding to that of the nystagmus. Nystagmus may disappear in chronic lesions as a result of adaptation, particularly with peripheral disease; however, its presence usually indicates an active disease process within the vestibular apparatus. Cats with bilateral vestibular disease do not have pathological or physiological nystagmus.

Caloric nystagmus is a type of physiological nystagmus that can be induced by irrigating the ear canal with ice-cold water (0° C) or warm water (44° C) for 3 to 5 minutes. The water causes the flow of endolymph within the ducts. Absence of response or asymmetry between sides may indicate vestibular dysfunction, but this often is too unreliable to use in the clinical case.[1,3,7]

Ataxia

Ataxia is a loss of muscular coordination or an irregularity of muscle action. It generally is associated with an abnormality of the cerebellar, vestibular, or proprioceptive pathways. Cats with vestibular dysfunction assume a wide-based stance and may

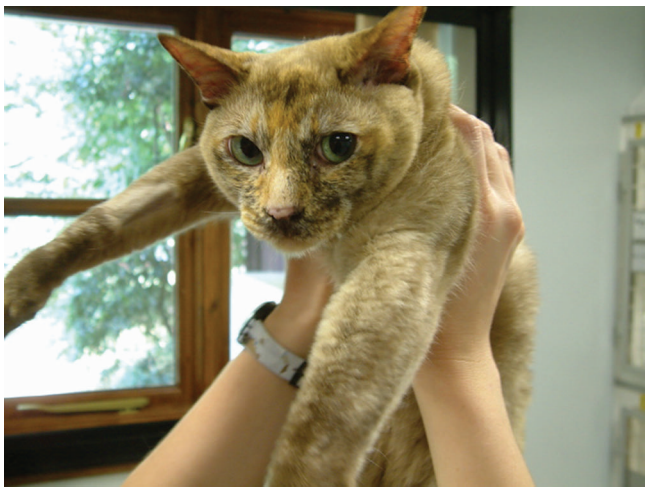


Figure 56-7. Physiological nystagmus can be assessed by lifting the cat to head height, moving it from side to side, and observing the cat's eyes for a coordinated response.

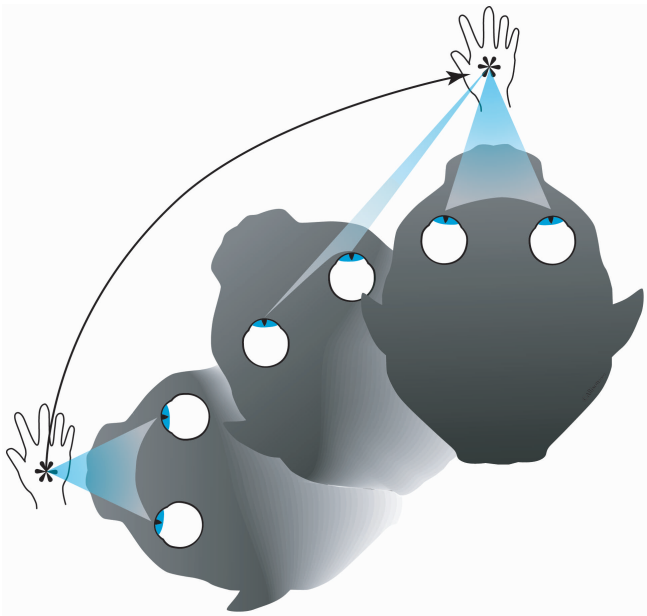


Figure 56-8. Physiological nystagmus assists with maintaining a fixed focus on a moving object. (From Platt S, Olby N: The manual of canine and feline neurology, ed 3, 2004, British Small Animal Veterinary Association.)

lean or drift toward the side of a lesion.* With disease of the flocculonodular lobe of the cerebellum or the supramedullary part of the caudal cerebellar peduncle, the ataxia may be directed to the side opposite the lesion as part of the paradoxical central vestibular syndrome. Cats with bilateral vestibular disease usually have a symmetrical ataxia and may fall to either side.

Positional Strabismus

Strabismus is an abnormal position of the eye and often is present in cats with vestibular disease. Strabismus can be induced when the head is moved dorsally and is thus termed positional; normally, when the head and neck are extended, the eye should remain centered within the palpebral fissure. The deviation often is ventral and lateral on the ipsilateral side but is not due to paralysis of any of the cranial nerves innervating the extraocular muscles of the eye.* The eyeball occasionally can be noted to deviate without extension of the head and neck, which appears as a lower motor neuron strabismus, corrected by inducing the patient to move its eyeballs to gaze in different directions.[10] The presence of positional strabismus does not help with the determination of a peripheral or central vestibular disease. Dysconjugate strabismus implies deviation of both eyes in different directions and is an uncommon finding, which may be more common with central disease. Rarely, the opposite eyeball exhibits a dorsal strabismus.[10]

*References 1,3,4,7,12,13.

Other Clinical Signs Associated with Vestibular Dysfunction

Facial Paresis or Paralysis and Hemifacial Spasm

Cranial nerve VII, the facial nerve, enters the internal acoustic meatus of the petrosal bone, and courses through the facial canal to exit the stylomastoid foramen located dorsal to the tympanic bulla.[1] Its course is near the components of the peripheral vestibular system and is affected commonly with destructive lesions to the peripheral vestibular system.[8] The resulting signs are those of facial paresis, paralysis, or more rarely spasm. The owners may report that the patient drools excessively or drops food from the mouth on the affected side. The menace response and palpebral and corneal reflexes often are reduced or absent because of an inability to close the eyelid.[1,3,7,14] Because the facial nerve also supplies preganglionic parasympathetic fibers to the lacrimal gland and salivary glands,[15] neurogenic keratoconjunctivitis sicca may accompany facial nerve paralysis associated with middle ear disease, in addition to the presence of xeromycteria.[1,7]

Hemifacial spasm may be seen early in the course of middle ear diseases.[8] Inflammation of the facial nerve may cause the facial muscles on the affected side to become hypertonic, causing the face and nose to be pulled caudally. A narrowed palpebral fissure may exist, which is caused by partial closure of the eyelids, elevation of the ear, and wrinkling of the face. These signs may precede those of facial paresis and paralysis.[8]

Horner's Syndrome

Horner's syndrome (miosis, ptosis, enophthalmos, and protrusion of the third eyelid) of the ipsilateral eye may be present with middle or inner ear disease, causing peripheral vestibular dysfunction (Figure 56-11).[1,3,16,17] This association is seen because the vagosympathetic trunk synapses in the cranial cervical ganglion deep to the tympanic bulla. The postganglionic fibers pass with the internal carotid artery into the middle ear cavity through the tympano-occipital fissure, which is in close proximity to the vestibulocochlear nerve (Figure 56-12).[15,16] Horner's syndrome is associated rarely with central vestibular syndrome.[1,3,7] Sympathetic hyperirritability has been reported in early otitis media, because of disease of the post-ganglionic sympathetic fibers resulting in dilation of the pupil[3,5,16] and exophthalmos.[18] This has been likened in human beings to Pourfour du Petit syndrome.[18]

*References 1,3,4,6,7,12,13.

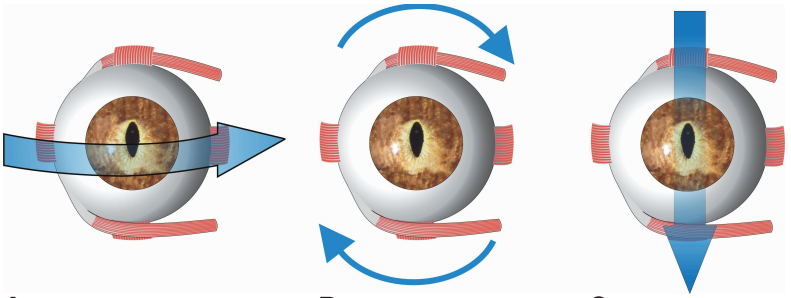


Figure 56-9. Nystagmus can be horizontal **(A),** rotary **(B),** or vertical **(C)** in its predominant direction. Vertical nystagmus is suggestive of a central vestibular lesion. (From Platt S, Olby N: The manual of canine and feline neurology, ed 3, 2004, British Small Animal Veterinary Association.)

Figure 56-10. Nystagmus induced when the cat is held in an unusual position, such as upside down, is called positional nystagmus.

Figure 56-11. Ipsilateral Horner's syndrome (miosis, ptosis, enophthalmos, and nictitating membrane protrusion) in a domestic long-haired cat.

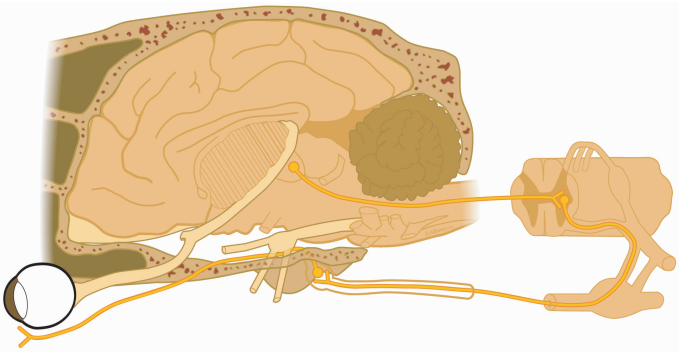


Figure 56-12. Schematic representation of the sympathetic innervation of the pupillary muscles of the eye. A lesion at any point in this pathway will cause an ipsilateral Horner's syndrome. (From Platt S, Olby N: The manual of canine and feline neurology, ed 3, 2004, British Small Animal Veterinary Association.)

Hemiparesis or Tetraparesis

Paresis suggests abnormal neurological function (weakness) without complete paralysis, which implies that some voluntary motion remains. Locomotion is thought to be initiated in the brainstem of animals, and so paresis usually is seen with any lesion within the neuraxis caudal to the level of the red nucleus in the midbrain.[7] With unilateral focal central vestibular diseases, paresis of the ipsilateral limbs (hemiparesis) may be seen if the motor pathways in the medulla oblongata also are affected. Large or multifocal lesions can cause an asymmetric tetraparesis. Strength always is maintained with peripheral vestibular dysfunction, which is a key finding on neurological examination.

Head Tremors

A tremor is an involuntary, rhythmic, oscillatory movement of all or part of the body.[7] It results from alternating contraction of antagonistic muscles of variable frequencies. Localized tremor usually involves the head and in most cases this is an intention tremor. Intention tremors occur commonly with goal-oriented tasks such as when an animal "intends" to perform a task such as eating or drinking. These tremors indicate underlying cerebellar dysfunction. Cerebellar dysfunction in conjunction with vestibular dysfunction implies central vestibular disease.

Altered Mentation

Disorders causing central vestibular dysfunction may be accompanied by altered mentation. The reticular activating system of the brainstem facilitates the alert-awake state in animals. Damage to this area may cause disorientation, stupor, or coma.[1,3,7] Peripheral vestibular disease often causes disorientation, which makes the assessment of mentation more difficult.

Multiple Cranial Nerve Dysfunction

Central vestibular syndrome may be accompanied by other cranial nerve dysfunction. Cranial nerves V, VI, VII, IX, X, and XII may be affected. Clinical signs suggesting involvement of these cranial nerves include ipsilateral facial hypalgesia, atrophy of the masticatory muscles, reduced jaw tone, facial paralysis, tongue weakness, and loss of the swallow or gag reflex. An ipsilateral loss of menace response accompanying vestibular dysfunction usually implies cranial nerve VII dysfunction, or multifocal disease affecting the forebrain or optic nerve. A loss of menace response also can be associated with cerebellar dysfunction.[19] Possible causes include an alteration of the menace response pathway from the visual cortex to the facial nucleus through the cerebellum or a loss of cerebellar influence on the cerebrocortical neurons.[1]

Circling, Leaning, and Falling

Falling or leaning toward the side of the lesion indicates asymmetrical vestibular disease. Cats with unilateral vestibular dysfunction show reduced extensor tone ipsilaterally and increased extensor tone contralaterally. This is manifested clinically as leaning, falling, and a tendency for tight circling toward the side of the lesion.* Shaking the head induces falling or leaning.

Decerebellate Posturing

Decerebellate posturing can be observed with severe and acute central vestibular dysfunction. This posture is characterized by opisthotonus with thoracic limb extension, normal mentation, and flexion of the pelvic limbs.[7] Decerebellate posturing can be intermittent and misinterpreted as seizure activity. Dorsiflexion of the neck sometimes elicits this posture in cats with cerebellar dysfunction.

Vomiting

The vomiting center is located within the reticular substance of the medulla, with direct connections to and from the vestibular nuclei.[1-5,7,12,13] Vomiting can occur in cats with acute vestibular dysfunction.

Deafness

Middle and/or inner ear disease also may cause hearing loss through conductive or sensorineural impairment, respectively. Conductive deafness occurs with impedance of sound wave transmission through the middle ear caused by structural defects such as ceruminoliths, a ruptured tympanum, bony ossicle damage, fluid accumulation, or aural neoplasms.[13,20,21] External ear canal lavage can affect hearing thresholds in dogs and the same is assumed for cats.[20] Sensorineural deafness results from abnormalities of the inner ear structures, cochlear nerve, or central auditory pathway.[13,22,23] Deafness associated with central disease is considered rare.

*References 1,3,4,7,12,13.

DIAGNOSTIC APPROACH

The diagnostic approach for a cat with vestibular dysfunction depends upon whether the neuroanatomical localization is peripheral or central (Figure 56-13). Signalment, assessment of the clinical history, and thorough physical and neurological examinations are essential.

Peripheral vestibular dysfunction results from disease of the middle and inner ear affecting the receptors in the labyrinth and the vestibular portion of cranial nerve VIII. Central vestibular dysfunction results from disease affecting the brainstem and or the cerebellum.

Testing procedures are performed in a logical sequence, which depends on the cost expenditure and amount of invasiveness. Diagnosis of a central vestibular disorder may require performance of most of the testing procedures (see Figure 56-13).

Minimum Data Base

Hematology, serum biochemistry, thyroid hormone testing, and urinalysis are useful to screen for other underlying metabolic disorders. Thoracic radiography and abdominal ultrasound are recommended in older cats or in cats with central vestibular dysfunction to evaluate for multisystemic disease or metastatic neoplasia. An ophthalmological examination may reveal evidence of inflammatory CNS disease. Serology can assist with the diagnosis of some infectious diseases.

Otoscopy and Pharyngeal Examination

Cats with peripheral vestibular disease require examination of the ears and pharynx under general anesthesia. Both ears should be examined with an otoscope. The tympanum is examined for color, texture, and integrity. Otitis media is suspected when the tympanum is dark gray or brown. An intact tympanum does not rule out otitis media; visualization of a ruptured tympanum without other associated abnormalities also is unreliable for diagnosis of otitis media. Bulging (convex appearance) of the tympanum can indicate fluid accumulation within the middle ear (see Figure 38-8), whereas retraction (and a concave appearance) suggests a partially filled middle ear with obstruction of the auditory tube.[24]

Examination of the pharynx may reveal evidence of inflammation, polyp formation from the eustachian tube, or other masses associated with the choanae.

Radiography

Radiography is useful for evaluation of the osseous tympanic bulla. Skull radiographs are performed under general anesthesia to achieve adequate positioning. Lateral, dorsoventral, ventrodorsal, and oblique views are advised for tympanic bullae

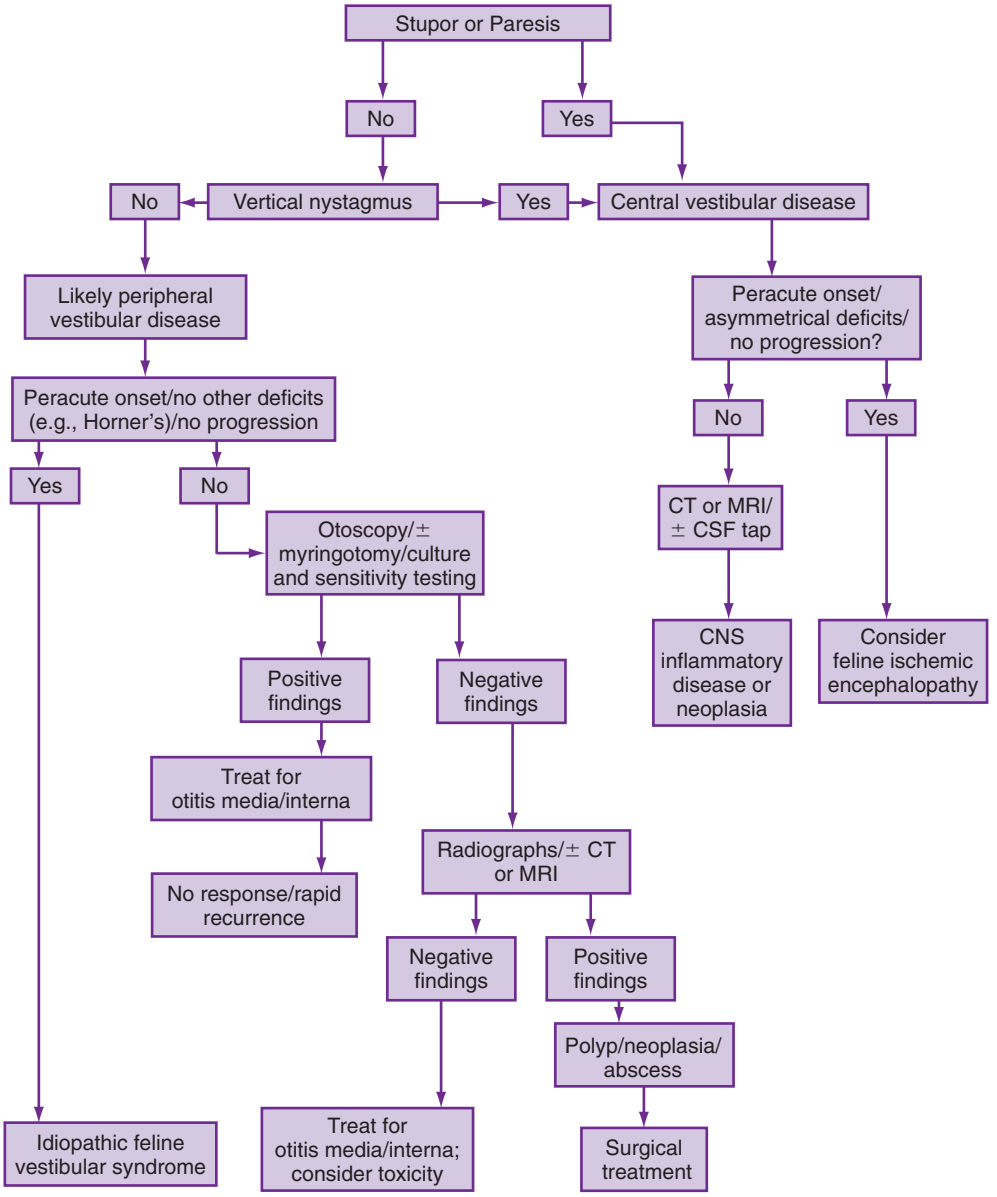


Figure 56-13. Algorithm to aid in the diagnostic approach of the vestibular cat.

assessments.[25] Positioning for radiography of the bullae has been described.[26] The normal tympanic bulla is a thin-walled gas-filled structure with well-defined, smooth borders.[26] Bilateral sclerosis of the bullae can be normal in older animals or a residual finding of previous ear disease. The external acoustic meatus is rounded with distinct smooth margins.

Myringotomy

Myringotomy is the deliberate puncture or incision through the tympanic membrane.[24] A 22-gauge spinal needle is used to puncture the ventrocaudal part of the tympanic membrane. The needle is connected to a 3-ml or 5-ml syringe, and fluid is aspirated for cytological analysis and culture.[24,27,28] Purulent or particulate matter within the middle ear may prevent needle aspiration and a larger hole may be needed for adequate drainage.[24] A myringotomy knife can be used to make a curvilinear or radial incision.[24] Care must be taken not to incise the tympanum too deeply and damage contents within the middle ear. Similarly, forceful flushing of the middle ear should be avoided. A normal tympanum heals within 21 to 35 days.[29]

Brainstem Auditory Evoked Potential

Brainstem auditory evoked potential (BAEP) testing is used to assess the integrity and function of the peripheral and central auditory pathways, and to evaluate the closely associated vestibular pathways indirectly.[30] BAEP are recordings of sound-evoked electrical activity in the auditory pathway between the cochlea and the auditory cortex. Because of the level of patient "cooperation" with cats, sedation or a light plane of general anesthesia often is needed for this test to be performed and interpreted properly. Small (27-gauge) needle electrodes are placed subcutaneously in the scalp and connected

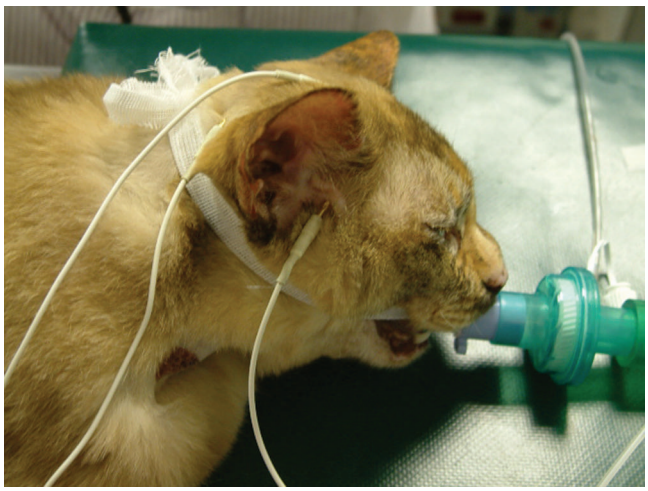


Figure 56-14. The typical recording set up for brainstem evoked potentials in the cat uses a monopolar recording electrode close to the vertex, a reference electrode at the mastoid just rostral to the base of the ear, and a ground electrode at the nuchal crest.

to sensitive amplifiers that can record signals in the microvolt range.[30] The electrodes are arranged with the positive electrode over the bregma on the dorsum of the skull, the negative electrode just rostral to the base of the pinna of the ear to be tested, and the reference electrode in the same position relative to the untested ear (Figure 56-14). The brain activity, resulting from broad-spectrum sounds, such as clicks delivered at 10 to 20 Hz through earphones inserted into the external ear canal, usually is averaged for 10 milliseconds (ms) for the early latency or brainstem potentials Averaging for 50 ms includes a record of middle latency responses, but these are not as well documented in cats.[31] The BAEP recording consists of six to seven positive time-locked peaks (I through VII) beginning at approximately 1 ms after the stimulation (Figure 56-15). Wave I represents acoustic nerve activity, and subsequent waves mark peak activities as sound is being processed through ascending portions of the auditory pathway (Figure 56-16). Mean latencies for peaks I, II, V, and VI in normal adult cats under sedation are 1.02 (±0.04), 1.84 (±0.04), 3.53 (±0.04), and 4.31 (±0.12) ms, respectively.[30] A lesion along the auditory pathway can cause an increase in the interpeak latencies (see Figure 56-15).

Cerebrospinal Fluid Analysis and Serology

Generally, cerebrospinal fluid (CSF) analysis is a useful adjunctive test for determination of the cause of central vestibular disease but rarely is specific. Risk of iatrogenic CNS trauma or cerebellar herniation after cisterna magna puncture in cats with space-occupying lesions should not be underestimated. Obtaining advanced imaging studies of the brain (see below) before CSF tapping is recommended, especially if a caudal fossa lesion is suspected. I frequently use a hypodermic needle for CSF acquisition in cats rather than a spinal needle and stilet to lessen risks of iatrogenic CNS damage.

Serology is useful for determining titers for presence of antigens but nonspecific for evaluation of antibody. Polymerase chain reaction analysis of CSF is now performed in specialized laboratories to evaluate for the presence of some infectious agents.[32]

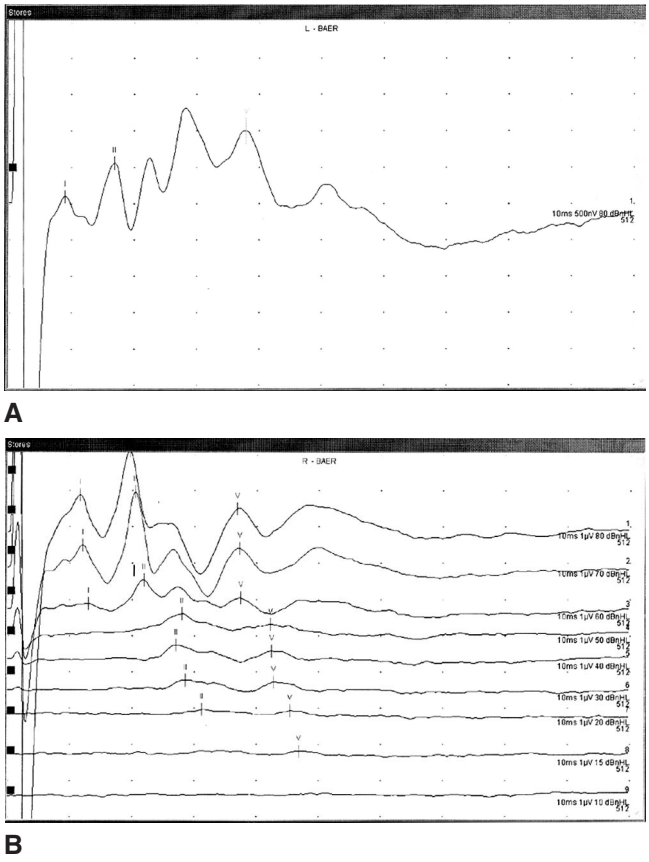


Figure 56-15. A, A typical waveform from a normal cat. **B,** Waveforms produced at decremental stimulus intensities demonstrate diminution of wave I to a point at which it becomes undetectable (50 dBnHL).

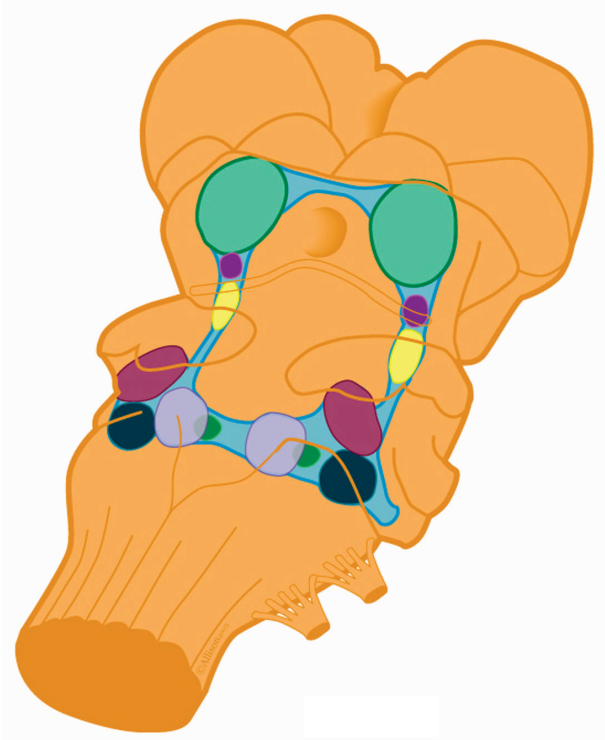


Figure 56-16. Schematic illustration of the nuclei within the brainstem purported to be responsible for the generation of the individual waveforms of the short-latency auditory evoked potentials.

Advanced Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) have revolutionized the diagnosis of vestibular diseases. The physics and interpretation details of both of these modalities have been described in detail.[33] CT evaluation of the peripheral vestibular system is particularly useful if radiographs have not determined an underlying cause, if nasopharyngeal polyps or neoplasia are suspected, or if the patient is a potential surgical candidate. The same interpretive principles used for the radiographic diagnosis of peripheral vestibular diseases apply to CT. Findings are more apparent on transverse CT images, however, because of reduced superimposition of structures in comparison to radiographs. CT can allow for an earlier diagnosis of subtle lesions. On a well-positioned study, both bullae should appear symmetrical, although subtle variations occur. Lumina of the tympanic bulla and the external ear canals are gas filled (see Figure 38-16). The tympanic bulla has a thin well-defined wall. Optimal resolution of the inner ear is achieved with high-resolution CT, but it still may be inferior to high-field MRI.

CT evaluation for central vestibular diseases is less helpful because of beam hardening artifacts. The density of the petrous temporal bones obliterates the visualization of the medulla.[33]

MRI is used less than radiography and CT for the diagnosis of peripheral vestibular disease because of its comparative limited availability and high cost. MRI allows for multiplanar views when compared to CT.[33] Improved soft tissue resolution allows for better assessment of neoplastic and inflammatory processes that affect the vestibular system. A typical MRI study consists of T1-weighted (T1W), T2-weighted (T2W), and proton density–weighted sequences.[34] Transverse, sagittal, and dorsal planes are used to evaluate the brain and cranium. A T1W sequence is obtained after intravenous administration of a gadolinium-based contrast agent.[34] Transverse and dorsal planes with T1W and T2W sequences are suggested for MRI of the middle ear in cats.[35] Post-contrast sequences are recommended if a mass is present in the tympanic bulla or external ear canal.

DIFFERENTIAL DIAGNOSES

Peripheral Vestibular Diseases

Anomalous Vestibular Diseases

Congenital vestibular disorders have been reported in Siamese and Burmese kittens (Tables 56-2 and 56-3).[36] Signs of peripheral vestibular dysfunction and concurrent deafness may be detected by 3 to 4 weeks of age and show clinical improvement within 3 to 4 months. A hereditary abnormality has not been proven. Diagnosis is based on history, excluding other causes, and BAEP results.

Neoplasms

Neoplasms that involve the peripheral vestibular system include squamous cell carcinoma, fibrosarcoma, osteosarcoma, chondrosarcoma, and ceruminous gland and sebaceous gland adenocarcinoma.[10] *Squamous cell carcinoma* is the most common malignant tumor of the middle and inner ear in cats.[37] Nonkeratinizing squamous epithelial cells are found normally in the eustachian tube and the middle and inner ear.[40]

Clinical signs of peripheral vestibular dysfunction have been documented but vary depending upon lesion extension.[38,39] Neoplasms of the middle/inner ear also can cause oropharyngeal signs that present with pain on palpation of the bulla or

Table 56-2 | **Differential Diagnostic Considerations for Peripheral and Central Vestibular Disease**

	SPECIFIC DISEASES	
DISEASE MECHANISM	**PERIPHERAL DISEASE**	**CENTRAL DISEASE**
Degenerative		Cerebellar cortical abiotrophy Lysosomal storage diseases
Anomalous	Congenital vestibular disease	
Nutritional		Thiamine deficiency
Neoplasia	Squamous cell carcinoma Fibrosarcoma Osteosarcoma Ceruminous gland or sebaceous gland adenocarcinoma	Medulloblastoma Oligodendroglioma Meningioma Lymphoma Extension of middle ear neoplasia Metastasis
Inflammatory/infectious	Bacterial otitis interna/labyrinthitis Cryptococcosis Nasopharyngeal polyps (*Cuterebra* larval migration)	See Table 56-3
Idiopathic	Idiopathic vestibular syndrome (*Cuterebra* larval migration)	
Toxic	Aminoglycosides Furosemide Bumetanide Chlorhexidine 10% fipronil solution (aural administration)	Metronidazole Lead
Traumatic	Iatrogenic External/middle ear flushing Bulla osteotomy Bulla fracture/hemorrhage	Head trauma
Vascular		Feline ischemic encephalopathy *Cuterebra* larval migration

Table 56-3 | **Inflammatory Central Nervous System Disorders of Cats That May Cause Vestibular Dysfunction**

CLASS OF ETIOLOGICAL AGENT	SPECIFIC DISEASE
Viral	Feline infectious peritonitis virus
	Feline immunodeficiency virus
	Feline leukemia virus
	Rabies
	Pseudorabies
	Borna disease virus
Protozoal	Toxoplasmosis
	Encephalitozoonosis
Bacterial	Aerobes
	Anaerobes
Fungal	Cryptococcosis
	Blastomycosis
	Histoplasmosis
	Coccidioidomycosis
	Aspergillosis
	Phaeohyphomycosis
Parasitic	Cuterebral larval myiasis
	Dirofilaria immitis
Agent unknown	Nonsuppurative meningoencephalomyelitis (presumed viral)
	Eosinophilic meningoencephalitis

From Muñana K: Inflammatory disorders of the central nervous system. In August JR, editor: Consultations in feline internal medicine, vol 4, Philadelphia, 2001, WB Saunders Co, pp 425-433.

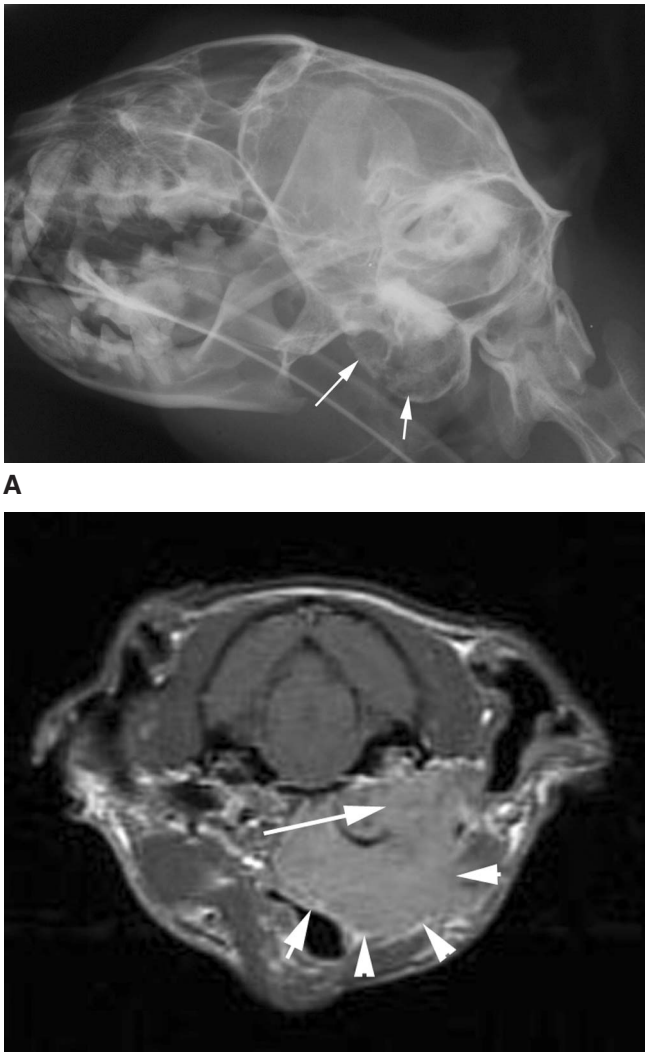


Figure 56-17. **A,** Lateral skull radiograph of a 9-year-old domestic shorthaired cat with evidence of bulla lysis *(arrows),* which was due to a middle ear squamous cell carcinoma. **B,** Transverse T1W contrast enhanced MRI of the same cat seen in Figure 56-17, *A*. A large slightly hyperintense mass can be identified originating from the bulla *(arrow)* with extensive invasion into the surrounding soft tissues. Approximate margins are delineated by arrowheads. (Courtesy Ruth Dennis MRCVS, Animal Health Trust, UK.)

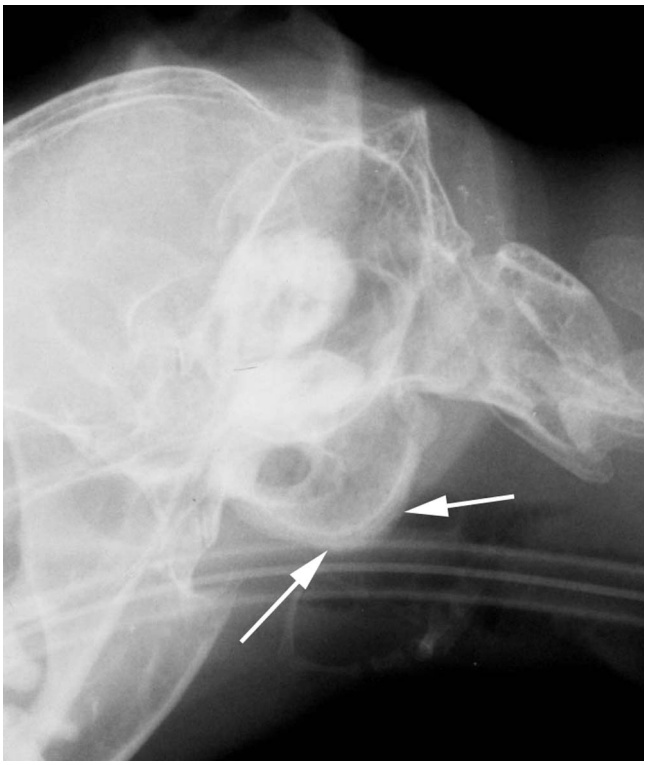
when manipulating the jaw. In addition to an examination of the external ear cavity and the tympanum for masses, the oropharynx should be examined for swelling or deviations of the soft palate.[40] Suspicious lesions should be aspirated for cytological analysis. Radiography of the skull can reveal soft tissue opacity in the tympanic bulla, osteolysis, and periosteal reaction (Figure 56-17).[26,41] CT is a more accurate method for determining lesion extent. Opacity within the tympanic bullae can indicate fluid or a soft tissue mass effect. Lesion extent within the horizonal and vertical ear canals is identified. Bony lysis involving osseous bulla, petrous temporal bone, and adjacent calvarium may be visualized with aggressive neoplasms.[25] Some neoplasms contrast enhance. MRI characteristics described for neoplasms of the middle ear include lysis of the osseous tympanic bulla and petrous temporal bone that can extend to adjacent structures.[42] However, a malignant melanoma involving the external ear canal and dorsalateral compartment of the tympanic bulla has been described in the cat, in which destruction of the bulla was not present and contrast enhancement of the mass did not occur.[35]

Radical surgical resection and adjunctive radiotherapy often is recommended as a treatment for neoplasms involving the middle ear. Median disease-free interval of 42 months has been reported for cats with ceruminous gland adenocarcinoma after surgery alone.[43]

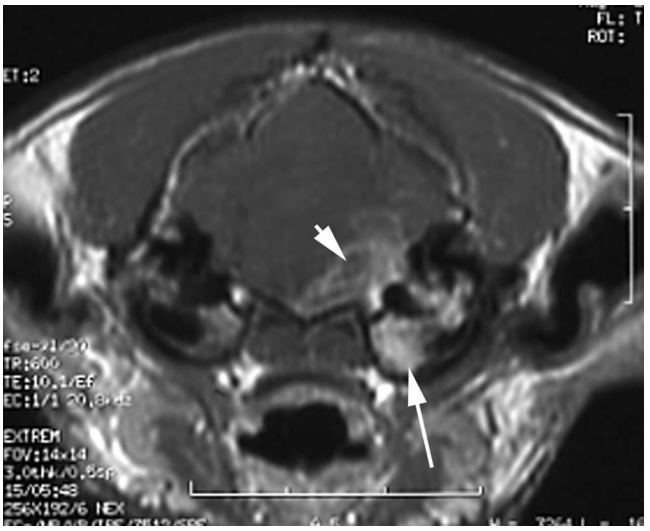
Inflammatory or Infectious Vestibular Diseases

Bacterial otitis interna or *labyrinthitis* can cause clinical signs of peripheral vestibular dysfunction. Often otitis interna and media occur concurrently. Organisms isolated commonly from the bullae include *Staphylococcus* spp., *Streptococcus* spp., *Pasteurella* spp., *Proteus* spp., *Escherichia coli, Enterococcus* spp., *Pseudomonas* spp., and obligate anaerobes. Yeast infections are an uncommon cause of otitis media.[44]

Diagnosis is based on otoscopic examination, myringotomy, and imaging. Otitis externa may be evident but is not necessarily the origin of the bacterial infection. Bulging and discoloration of the tympanum may be identified if the bulla contains fluid or an exudate. Fluid within the middle ear can be collected by myringotomy for cytological examination and anaerobic and aerobic culture/sensitivity.[36] The external ear canal also is cultured. Skull radiography is performed with the cat under general anesthesia. The latero-20-degree ventrolaterodorsal oblique and rostral-30-degree ventral-caudodorsal open-mouth oblique views are best for evaluation of the tympanic bullae.[41] Common radiographic findings associated with otitis



A



B

Figure 56-18. A, A lateral oblique skull radiograph of a 4-year-old domestic short-haired cat with severe otitis media/interna. Extensive periosteal proliferation of the osseous bulla is present *(arrows)*. **B,** A transverse T2W image of the caudal fossa of a 10-year-old domestic short-hair cat with severe otitis media/interna *(arrow)*. This infection has extended intracranially into the ipsilateral brainstem *(arrowhead)*. (*A,* courtesy of Ruth Dennis MRCVS, Animal Health Trust, UK.)

media/interna include soft tissue opacity in the bulla and/or petrous temporal bone and bony proliferation of the petrous temporal bone (Figure 56-18).[26] If the infection is severe enough, lysis of the tympanic bullae also can be visible.

CT findings with otitis media/interna include thickening and irregularity of the tympanic bulla wall, lysis of the bulla, and radiopacity within the bulla, which suggests fluid or a soft tissue mass[25] (see Figure 38-16, *B*). A study that compared CT with radiography for diagnosis of otitis media/interna found CT to have 11 per cent false-positives and 17 per cent false-negatives for diagnosis confirmed by surgical findings. CT was a more sensitive but less specific technique than skull radiography.[45,46] Neither radiography nor CT was able to detect early lesions associated with otitis media/interna when no osseous involvement occurred. Otitis interna is difficult to assess with CT except in cases of severe destruction of the inner ear. MRI findings that are compatible with otitis media include medium-signal intensity material in the tympanic bulla on a T1W sequence and hyperintense on a T2W sequence.[25] The inner margin of the tympanic bulla also may enhance after gadolinium administration.[42]

Osseous lesions of the tympanic bulla are more difficult to assess with MRI. An MRI finding of otitis interna is a lack of signal intensity of the labyrinthine fluid on T2W sequences.[42] This may represent replacement of the fluid with fibrous tissue; however, similar findings are seen in normal ears. Meningeal enhancement on post-contrast T1W sequences also has been described secondary to otitis interna.[47]

Treatment consists of long-term (6 to 8 weeks) antibiotic therapy and prognosis usually is good. Improvement often occurs within 1 to 2 weeks of therapy. Refractory cases may require surgical drainage of the tympanic bulla.[36,48]

Cryptococcosis more often causes central vestibular dysfunction. However, three cats have been reported with peripheral vestibular disease referable to otitis media/interna because of cryptococcosis.[49] The infection was isolated from the tympanic bulla in two cats and the eustachian tube in one cat. All cats responded well to surgical drainage and medical therapy.[49]

Nasopharyngeal polyps are pedunculated masses that can arise from the epithelial lining of the tympanic cavity, eustachian tube, or nasopharynx.[44,50,51] Nonseptic otitis media/interna may occur secondary to occlusion of the eustachian tube because of a nasopharyngeal polyp, and polyps may occur as a result of chronic middle ear infection or from ascending infection from the nasopharynx.[44,52] Polyps are especially common in young adult to middle-age cats, with no apparent gender or breed predisposition. Clinical signs include peripheral vestibular dysfunction, head-shaking, aural discharge, facial nerve paralysis, and Horner's syndrome.[44] Clinical signs of nasopharyngeal involvement include dysphagia, stertorous respiration, respiratory distress, and change in phonation. A secondary suppurative meningoencephalitis has been documented in a young cat with lesion extension of an inflammatory polyp within the tympanic bulla.[53]

Inflammatory polyps of the middle ear can be visualized using otoscopy or by inspection of the oropharynx with the cat under general anesthesia. A lateral skull radiograph can reveal a soft tissue mass in the nasopharyngeal area and assist with the identification of nasopharyngeal polyps (Figure 56-19).[25] Other radiographic findings associated with polyps include unilateral or bilateral soft tissue opacity within the tympanic bulla and sclerosis of the osseous bulla.[26,41] Transverse, sagittal, and parasagittal CT images of nasopharyngeal polyps in cats have been described.[53,54] CT can lateralize the lesion and assess the lesion extent.

MRI of polyps is recommended because of the superior soft tissue resolution of this modality. Two cases of inflammatory polyps have been described in which signal intensity on post-contrast T1W sequences was increased.[35] In one cat, a

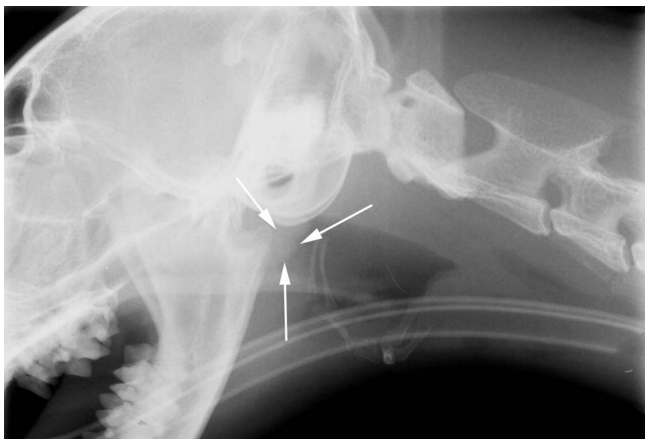


Figure 56-19. A lateral skull radiograph of a 7-year-old domestic shorthaired cat with a nasopharyngeal polyp *(arrows)*. (Courtesy Ruth Dennis MRCVS, Animal Health Trust, UK.)

nonuniform increase occurred in signal intensity on T2W sequences.[35]

Treatment involves traction and avulsion of the mass through the external acoustic meatus or from the nasopharyngeal cavity.[55] Bulla osteotomy can facilitate polyp removal from the tympanic bulla. Prognosis usually is good, although a residual head tilt is not uncommon.[56] The recurrence rate after polyp removal is approximately 40 per cent. Recurrence is more likely in cats with aural polyps and more severe signs of otitis externa and less likely if treated with steroids after surgery.[57]

Idiopathic Feline Vestibular Syndrome

Idiopathic feline vestibular syndrome (IFVS) is a disease of peracute peripheral vestibular dysfunction (less than 24 hours). The incidence is highest during the months of July and August in the United States.[58] No sex predilection exists, and the median age of 75 affected cats in one study was 4 years.[58] No confirmed cause exists; however, as in Meniere's disease in human beings, abnormal endolymphatic flow or electrolyte aberrations in the perilymph have been hypothesized.[58]

With lack of a structural lesion, other associated neurological deficits such as Horner's syndrome or facial nerve paralysis would not be expected.[58] Bilateral disease can occur but this is uncommon (less than 10 per cent).[58]

Clinical signs of IFVS often are preceded by upper respiratory tract disease[10]; additionally, excessive vocalization can be seen, which probably is due to the generalized feeling of disorientation.[58] Diagnosis of IFVS is made through exclusion of other causes of peripheral vestibular disease (see Table 56-1). No specific treatment exists for IFVS besides managing the clinical signs such as anorexia, which may accompany this condition. Prognosis for spontaneous recovery is good although this may take 2 to 4 weeks, and 25 per cent of affected cats may have residual deficits such as a head tilt.[58] I have seen recurrence of signs with IFVS to be more common in cats than dogs with idiopathic vestibular disease.

Cats with CNS cuterebriasis have been documented to present most commonly during the months that coincide with the occurrence of IFVS.[58,59] This similarity has led to the hypothesis that *Cuterebra* larval migration may account for some idiopathic vestibular cases in cats in the United States. However, clinical signs of CNS cuterebriasis and idiopathic vestibular disease are dissimilar, and most cats with idiopathic vestibular disease recover in a few weeks, which makes this hypothesis less plausible. Migration of a *Cuterebra* larva through the ear canal to the peripheral vestibular apparatus still remains as a potential cause of peripheral vestibular disease.

Toxic-Related Vestibular Disease

Peripheral vestibular disease can be caused by ototoxic agents. An ototoxic agent is a substance that can produce cochlear or vestibular damage by causing unilateral or bilateral damage to structures of the inner ear.[60] Parenteral or oral administration of ototoxic drugs reaches the structures of the inner ear by the hematogenous route. Topical drugs applied into the external ear canal reach the middle ear through a ruptured tympanic membrane and subsequent penetration into the inner ear via the round or oval window. The membrane of the round window is more permeable to macromolecules when otitis media is present.[60] The ototoxic substance passes into the perilymph, which is contiguous within the osseous labyrinths of the cochlea and vestibule.

Many agents are listed in the literature as "potentially" ototoxic, but much of the information is based on anecdotal reports. Studies also are extrapolated from species other than cats, and use dose formulations that far exceed the concentrations in proprietary medication. As an example, chlorhexidine and gentamycin often are quoted as ototoxic drugs when administered topically; however, no vestibular abnormalities were seen when these drugs solutions were administered at 0.2 per cent and 0.3 per cent concentrations, respectively.[60] A list of potential ototoxic agents for cats is shown in Table 56-2.

Aminoglycosides can damage the neuroepithelium of the macule and crista of the vestibular apparatus, in addition to the hearing apparatus. The severity of vestibular toxicity may be directly proportional to the duration and concentration of aminoglycoside given.[60,61]

Other antibiotics, such as erythromycin, minocycline, chloramphenicol, vancomycin, and topical polymyxin B, have been reported to cause vestibular damage in human beings, but this has not been observed in cats.[60]

Loop diuretics (e.g., furosemide) cause ototoxicity in human beings, but this has not been reported in cats when standard clinical doses have been prescribed.[60]

Regarding *antiseptics,* many studies have been performed to document the ototoxic effect of intratympanic application of chlorhexidine. At 2 per cent concentration, chlorhexidine is obviously ototoxic to the cochlea and vestibular system, but the damage is much more subtle at 0.05 per cent, and no clinical effects are seen.[60]

Peripheral vestibular disease has been reported after the off-label use of intraaural 10 per cent fipronil solution for otoacariosis in two cats.[62] The cats developed vestibular dysfunction and signs of Horner's syndrome within 6 hours after two drops of the solution were administered in each ear.[63] Both cats showed signs of improvement within 5 days, but one of the cats had a residual head tilt.

Diagnosis of toxicity in peripheral vestibular disease is based on history and results of otoscopic examination and BAEP testing. Treatment consists of cessation of the ototoxic

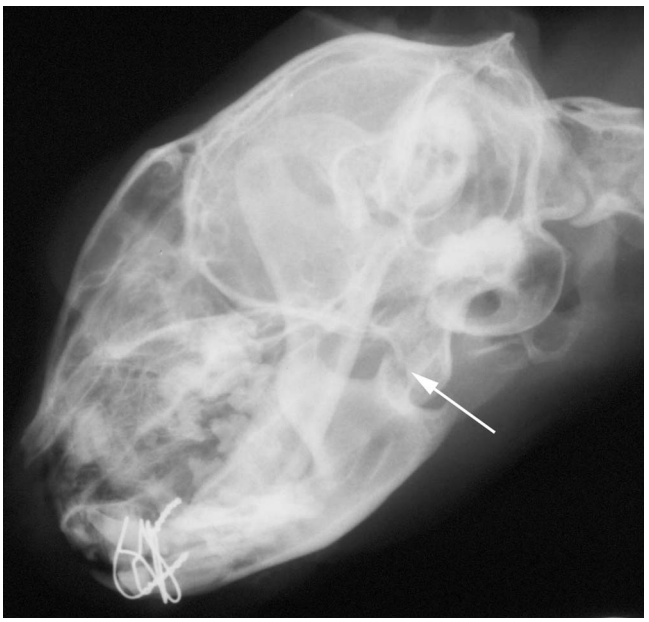


Figure 56-20. A lateral oblique radiograph of a 9-year-old cat with severe head trauma and peripheral vestibular syndrome after being hit by a car. No evident trauma was identified in the bullae, but the severity of the trauma to this area of the head can be estimated from the nearby fracture of the temporomandibular condyle *(arrow).* (Courtesy Ruth Dennis MRCVS, Animal Health Trust, UK.)

agent and initiation of supportive care. Prognosis for recovery from the vestibular signs is good in most instances.

Trauma

CRANIAL TRAUMA. Peripheral vestibular signs may follow any trauma to the head, secondary to a fracture of the petrosal part of the temporal bone or tympanic bulla.[10] This often is accompanied by facial paresis/paralysis. Skull radiography or advanced imaging will be necessary for an accurate diagnosis (Figure 56-20). Treatment is supportive and should be focused on any concurrent injuries sustained during the trauma.

IATROGENIC TRAUMA. Peripheral vestibular disease can be seen immediately after a bulla osteotomy, especially in cases of vigorous curettage of the petrous temporal bone.[64] Supportive care and appropriate antibiosis are necessary, but resolution usually occurs because of compensation by the animal. Three cats with signs of unilateral ocular sympathetic hyperactivity (mydriasis and exophthalmos) have been reported after middle ear flushing procedures; however, the cats had signs of peripheral vestibular dysfunction because of otitis media/interna before the procedure.[18]

Central Vestibular Diseases

Degenerative Diseases

CEREBELLAR CORTICAL ABIOTROPHY. In contrast to dogs, this condition in cats is exceedingly rare. Sporadic anecdotal cases have been mentioned in the literature.[65] Late-onset cerebellar abiotrophy has been documented in adult cats,[66] but it would be expected primarily in kittens.[67,68]

LYSOSOMAL STORAGE DISEASES. Specific lysosomal storage disorders have been reviewed (see *Consultations in Feline Internal Medicine,* volume 4, chapter 51).[69] Lysosomal storage diseases documented to cause central vestibular disease include GM1-gangliosidosis, Niemann-Pick disease type C (sphingomyelinosis), and alpha-mannosidosis.

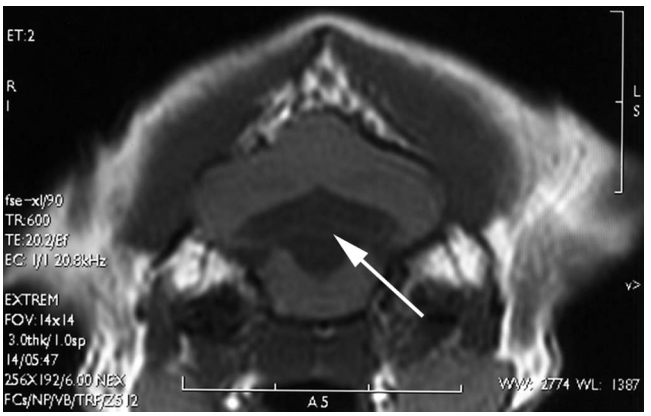


Figure 56-21. A transverse T2W MRI of a 2-year-old domestic shorthair cat with dilation of the fourth ventricle *(arrow)* and subsequent secondary changes in the medulla and overlying cerebellum.

Anomalous Vestibular Diseases

HYDROCEPHALUS. This disease is not common in cats but may be the result of obstructive processes such as neoplasia or inflammation elsewhere in the neuraxis. Enlargement of the fourth ventricle may cause central vestibular dysfunction because of the anatomical location of the vestibular nuclei. Diagnosis requires advanced imaging (Figure 56-21), but a CSF tap also would be warranted to rule out an underlying inflammatory disease. Treatment is possible with either the use of prednisone (0.5 mg/kg PO q12h) or surgical placement of a ventriculoperitoneal shunt.

Nutritional Diseases

THIAMINE DEFICIENCY. This is the most common nutritional deficiency affecting the CNS, usually resulting in lesions of the oculomotor and vestibular nuclei, the caudal colliculus, and lateral geniculate nucleus.[44] The earliest neurological sign is vestibular ataxia, progressing to seizures, dilated nonresponsive pupils, and ultimately coma.[36] Treatment is administration of thiamine, parenterally (100 to 250 mg q12h) or intravenously.[36,44]

Neoplasms

Neoplasms can affect the medulla of the brainstem or vestibular pathways associated with the cerebellum directly (parenchymal compression or invasion) or indirectly to cause central vestibular dysfunction. Neoplasms can affect these regions indirectly by (1) causing an obstructive hydrocephalus affecting the fourth ventricle and/or (2) increasing intracranial pressure, causing a rostrocaudal shift of the forebrain and/or hindbrain with subsequent cerebellar herniation through the foramen magnum. Space-occupying lesions in the region of the cerebellomedullary pontine angle often can be responsible for paradoxical vestibular syndrome.[10,19] Rarely, middle ear tumors in cats may extend medially to involve the brainstem.[37]

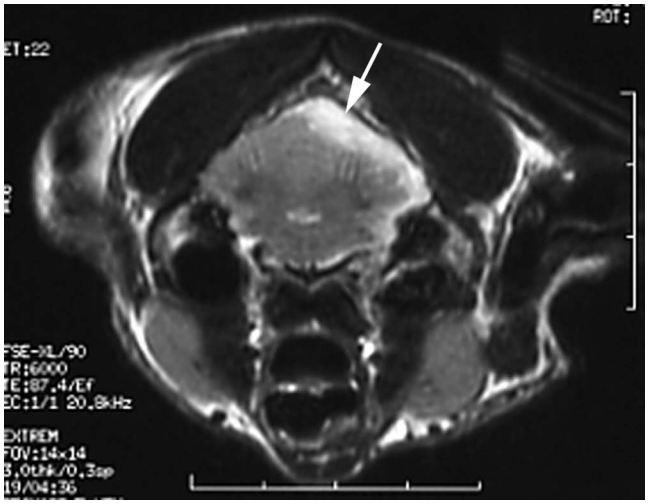


Figure 56-22. A transverse T2W MRI of a 4-year-old Burmese cat with extension of an otitis media/interna into the intracranial cavity. Hyperintense material, confirmed to be pus at surgery, can be seen adjacent to the cerebellum in the caudal fossa *(arrow)*.

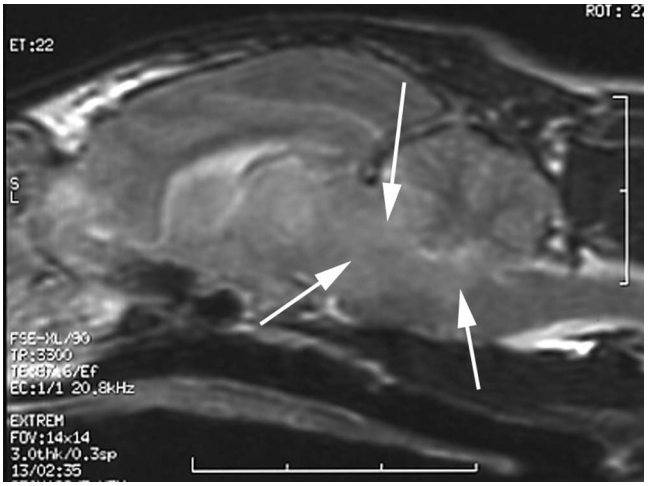


Figure 56-23. A sagittal T2W MRI of an 18-month-old domestic longhaired cat with a large irregular hyperintense lesion in the brainstem *(arrows)*. The lesion is not specific for *Toxoplasma* infection, which was confirmed on postmortem examination; the lesion could even represent a diffuse neoplastic lesion in this region, such as lymphoma.

The most common neoplasms in cats that affect this region are meningioma and lymphoma, but a cerebellar oligodendroglioma causing paradoxical signs also has been described in the cat.[19,70-72] In a study of 137 intracranial tumors in cats, five meningiomas, 12 lymphomas, and three glial cell tumors were documented to occur in the region of the cerebellomedullary angle and the region of the fourth ventricle. Although meningiomas have been observed in cats from 1 to 24 years of age, the majority of cats are older than 10 years.[70,72] The imaging characteristics of feline meningiomas have been well described (Figure 56-22).[19,73] Surgical resection of tumors in this area is challenging but can be achieved with improvement of the clinical signs, although recurrence is common[19] (see Chapter 54).

A 2-year-old cat has been diagnosed with a medulloblastoma, a type of primitive neuroectodermal tumor.[75] The cat presented with a 3-month history of an ipsilateral ataxia, which progressed to develop nystagmus, ipsilateral paresis, and dysmetria. Magnetic resonance imaging using a T1W sequence demonstrated an irregularly shaped hypointense mass within the cerebellar parenchyma that contrast-enhanced and was irregularly hyperintense on T2W images. Surgical resection was possible but no follow-up was documented.[75] The same cat seems to have been described in another report, which documented a 45-day postsurgery survival.[76]

Inflammatory or Infectious Vestibular Diseases

Any inflammatory disease that affects the CNS has the potential to cause central vestibular signs, usually as part of a multifocal syndrome. These diseases have been discussed in detail and are documented in Table 56-3.[77] The more common infectious agents are discussed briefly.

BACTERIAL MENINGOENCEPHALITIS/ABSCESSATION. Bacterial meningoencephalitis/abscessation from otitis media and otitis interna can extend into the intracranial cavity and result in bacterial meningoencephalitis[78] (see Chapter 53). Seven such cats with otitis media/interna have been documented, in one study, with CNS dysfunction that included central vestibular signs.[78] MRI was extremely effective in demonstrating the location, extent, and relationship to normal structures of inflammation of the middle ear and brainstem in all cases. A mild to severe neutrophilic pleocytosis was present in the CSF of four of five cats tested. Marked neurological improvement was seen in all the cats, which underwent surgical drainage in addition to prolonged antibiotic therapy.[78] Extension of bacterial infection into the CNS also has been documented in a 15-month-old male Maine Coon cat with an inflammatory polyp of the middle ear.[53] The cat required a ventral bulla osteotomy to remove the polyp in addition to broad-spectrum antibiotic therapy for the secondary suppurative meningoencephalitis but made a good recovery with a residual head tilt.

MRI is useful in detecting brain abscessation secondary to otitis media/interna.[25] Abscessation with extension of an inner ear infection can affect the brainstem and has a heterogenous signal intensity on T1W and T2W images (Figure 56-23). A ring-enhancing lesion with extension into the tympanic bulla can be seen after intravenous contrast administration.[79]

FELINE INFECTIOUS PERITONITIS. Feline infectious peritonitis (FIP) results from infection with a mutated form of feline enteric coronavirus and represents the most common cause of inflammatory brain disease in cats.[77] Neurological disease usually is seen with the noneffusive form of FIP, and up to a third of cats with this form of disease develop neurological disease.[80] Some affected cats have evidence of disease only localized to the CNS. Insidious multifocal or diffuse CNS clinical signs are seen, which commonly include vestibular dysfunction. Analysis of CSF is the most useful antemortem diagnostic test, which often reveals a neutrophilic pleocytosis with a marked protein elevation (more than 200 mg/dL).[77] However, this test cannot be relied upon to be either sensitive or specific for FIP. Positive coronavirus antibody titers in the CSF are the most reliable indicator of the disease,[80] but only if an albumin quotient and IgG index rule out serum protein translocation across a disrupted blood-brain barrier. Polymerase chain reaction (PCR) testing of the CSF recently has become available; unfortunately, only a third of cats with neurological FIP have

positive CSF PCR results, and only two thirds of brain tissue specimens actually are PCR-positive.[80] Advanced imaging reveals the presence of hydrocephalus in the majority of affected cats.[77] No documented effective treatment exists, and the prognosis is poor.

TOXOPLASMOSIS. Cats are the definitive hosts of *Toxoplasma gondii*. Occasionally, cats develop central neurological disease because of this organism. After the initial enteroepithelial life cycle, tachyzoites are disseminated through the blood and lymph. The immune system generally can suppress proliferation of tachyzoites with subsequent development of cysts. These cysts remain dormant for long periods and have a predilection for sites such as the brain.[77] Diseases associated with toxoplasmosis can be due to recrudescence of local infection. Multifocal neurological signs are a common clinical manifestation.

A definitive diagnosis is difficult. CSF analysis reveals a mixed pleocytosis and elevated protein levels. Comparison of CSF and serum antibody titers may aid in the diagnosis of the disease. PCR analysis for protozoal disease on the CSF is now available but may not be highly sensitive. Advanced imaging can reveal multifocal areas of irregular contrast-enhancing lesions within the brain parenchyma. Clindamycin (12.5 mg/kg PO q12h for 4 to 6 weeks) is advocated for treatment of this disease; however, the prognosis is guarded and residual signs and recrudescence may be common.[77]

CRYPTOCOCCOSIS. Cryptococcosis is the most common systemic mycosis of cats. Feline cryptococcosis has been reviewed extensively.[81] More than 80 per cent of cats present with signs of nasal cavity disease, including sneezing, nasal discharge, respiratory stridor, and subcutaneous masses at the nostrils (see Figure 38-5). The CNS occasionally is involved, manifesting with multifocal neurological signs, including central vestibular dysfunction. CSF analysis is the most helpful diagnostic test in cats with CNS cryptococcosis. The organism may be identified cytologically or cultured from the CSF. A positive capsular antigen test can provide a definitive diagnosis.[77] Treatment consists of triazole drugs (fluconazole, itraconazole) for at least 2 months beyond resolution of the clinical signs.[77] Fluconazole crosses the blood-brain-barrier readily and is the preferred antifungal agent. The decision to discontinue therapy is based upon repeat CSF analysis results, serology, and resolution of clinical signs. Often patients require long-term antifungal therapy. Prognosis is considered guarded.

Toxic-Associated Vestibular Diseases

METRONIDAZOLE. Although not common, central vestibular signs have been reported in cats after chronic high-dose therapy with metronidazole.[82] Clinical signs reversed in two of the cats reported within a few days of drug withdrawal and with appropriate supportive care.[82] Diazepam administration has improved the recovery time in dogs with metronidazole toxicity; this remains to be determined for cats. Unlike metronidazole toxicosis in dogs, nystagmus is an uncommon clinical finding.

LEAD. The most common clinical signs of lead toxicosis in cats are anorexia, vomiting, and seizures. Central vestibular abnormalities, including vertical nystagmus and ataxia, have been reported.[83] Old paint is the most common source of exposure for cats. Recovery can be complete after standard treatment.[83]

Trauma

Central vestibular signs subsequent to head trauma often imply brainstem involvement; occasionally, the signs may be due to elevated intracranial pressure, causing a rostrocaudal transtentorial herniation or a cerebellar herniation through the foramen magnum.

Diagnosis is supported by history and skull fractures on radiographs; however, it is not necessary for the skull to be fractured for central vestibular damage to occur. Advanced imaging studies can be used to assess for intracranial hemorrhage and edema. Principles for management of head trauma address the pathophysiologic sequelae to traumatic brain injury such as edema.

Vascular Diseases

FELINE ISCHEMIC ENCEPHALOPATHY (FIE). FIE is a poorly understood syndrome of brain infarction in cats. Onset of clinical signs is peracute. FIE affects cats of all ages and most commonly in the months of July and August. The main clinical signs are acute in onset, focal, and lateralizing; these include depression, blindness, circling, and central vestibular dysfunction.[84] This has been associated with *Cuterebra* spp. migration. Although central vestibular signs have been reported with this abnormality, other neurological signs supportive of forebrain disease are more common.[85] Diagnosis is based on focal lesions identified by advanced imaging and CSF analysis. Treatment is supportive care. Gradual improvement of clinical signs can occur over several months, but residual signs are likely. Severe cases can be fatal.

SUMMARY FOR TREATMENT OF VESTIBULAR DISORDERS

The damaged vestibular system can compensate over time with central reprogramming of eye movements and postural responses in addition to reliance on visual and other sensory input that replaces lost vestibular input.[3,7,12] Histamine is thought to be involved in the recovery of vestibular function, although the mechanism is unclear.[86]

If the underlying disease process can be targeted, the prognosis for a functional recovery can be good. Residual signs, such as a head tilt, are not uncommon. Recurrence of vestibular dysfunction can occur at times of stress, recurrent disease, or after an anesthetic episode.

Supportive care often is essential in cats with vestibular dysfunction, because anorexia is a frequent complication. Vomiting, salivation, and possible nausea associated with vestibular disease can be treated medically. Drugs used commonly include the phenothiazine derivative chlorpromazine (0.2 to 0.4 mg/kg SQ q8h); and the antihistamines diphenhydramine (2 to 4 mg/kg PO or IM q8h), dimenhydrinate (4 to 8 mg/kg PO q8h), and meclizine (12.5 mg q24h). Betahistine dihydrochloride is a histamine-like substance that is used in human beings with Meniere's syndrome and also has been shown to accelerate the recovery process from a central vestibular syndrome in experimental cats when used at daily doses of 50 mg/kg.[87] Clinical use has not been documented.

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Chapter 57

Safety of Blood Products for the Feline Patient

Anne S. Hale

Anemia, coagulopathy, and hypoproteinemia are common disease consequences in feline patients. The feline practitioner often finds the inclusion of transfusion therapy in his or her management plan. Transfusion therapy is not a new practice option; however, developments in the field of transfusion medicine in the last 10 years have increased the availability of transfusion products. Identification of donors, recognition of infectious disease, and collection of blood components are areas that have advanced significantly, which makes the use of blood products a reasonable and commonplace therapeutic strategy for the feline practitioner. As the science of transfusion medicine has progressed, the concern for safety of blood products has moved to the forefront. Areas related to safety of a blood product include donor evaluation, record keeping, infectious disease screening, advanced storage techniques, and recognition of transfusion reactions.

Veterinary transfusion medicine has mirrored the progression of the human blood banking industry. First, concerns were related largely to defining the science responsible for transfusion compatibility. Second, efforts shifted toward the standardization of blood product production. Finally, the industry has turned interest toward quality assurance and control. The AIDS pandemic in the early 1980s led to an extensive review of human blood component evaluation and screening. Currently, the Food and Drug Administration (FDA) oversees human blood supply in the United States. Groups such as the American Association of Blood Banks have developed extensive certification programs to ensure quality control and safety in the human blood supply.[1] The United States government does not regulate the animal blood supply. However, two organizations are now in existence for the purpose of self-regulating the industry and furthering the science of veterinary transfusion medicine: The Association of Veterinary Hematology and Transfusion Medicine (http://www.vetmed.wsu.edu/org-AVHTM) and The American Association of Veterinary Blood Banks (http://www.aavbb.org).

OVERVIEW

Safety of blood supply is related to careful donor evaluation, thorough record keeping, extensive infectious disease screening, intensive quality assurance for storage and transport, and avoidance of transfusion reactions. Evaluating safety of the feline blood supply reveals some unique features. The size of the average domestic cat makes "borrowing" technology from human transfusion medicine difficult. For larger companion animals, veterinary blood bankers have utilized blood collection techniques and systems used in the human industry. The total blood volume (325 ml) of the average 10-pound cat is less than the total volume of a standard human collection set (450 ml). Therefore FDA-approved, closed-system collection sets are not available for use with feline donors. Use of an open system for collection, most commonly a 60-ml syringe and butterfly catheter, can lead to bacterial contamination of the end product. Coincidentally, bacterial contamination with *Serratia marcescens* in feline units is the only published incident of external contamination of transfusion products in the veterinary literature.[2]

The feline donor may not be a willing volunteer. This unwillingness frequently adds the necessity for chemical restraint through sedation or anesthesia; most veterinarians who collect whole blood units from cats use anesthesia. Ketamine and diazepam continue to be a routine choice for restraint during blood donation. Concerns for the donor's ability to maintain a normotensive state during the procedure have led to exploration of other types of sedation or anesthesia. Isoflurane gas anesthesia may be used to avoid hypotension associated with most intravenous anesthetics. The presence of these drugs and stress-induced cytokines in the end product must be considered. Traditionally, safety of blood products has been limited to monitoring the "out-of-body" experience of the product from donor to recipient.[3] These issues surrounding the donor add an additional layer to the safety concerns that a feline blood banker must evaluate and resolve.

DONOR EVALUATION

Taking the History

Providing a safe feline blood supply starts with donor selection. Unlike our human counterparts, feline blood bankers cannot ask for a detailed history from the donor about their recent travel, sexual activities, drug usage, and illnesses. When

"volunteer" donors are used, an extensive questionnaire is recommended so that the owner can provide as much historical detail as possible. All commercial blood banks currently producing feline components control their feline donor pool strictly. Most have closed colonies of cats to allow a reliable means of detailing historical travel, drug administration, illness, and sexual activity.

Performing the Physical Examination

Physical evaluation of the donor perhaps is more important because we are unable to certify historical data. Feline donors are screened carefully for ectoparasites, evidence of bacterial disease, and normal physiological parameters. Any deviation from normal limits should exclude the donor from use. Note that evidence of bacterial disease includes periodontal disease, chronic urinary tract infection, or open wounds less than 72 hours old.[4] Presence of external parasites represents the potential exposure to infectious disease and should exclude the donor from use until the cat has been free of ectoparasites for a minimum of 30 days. Once again, because of the lack of direct information about the donor, biochemical screening before use is recommended. A complete blood count is a necessity. Abnormal cell types, indications of inflammation, low normal red blood cell count, and/or thrombocytopenia exclude donors from use.

Record Keeping

Record keeping must be thorough. Using a standard operating procedure to perform feline selection, phlebotomy, and collection minimizes risk of contamination, increases the proficiency of collection, and documents the process to provide accountability. Each unit of blood is tracked from donor to recipient. Labeling of blood products includes the proper identification of the component, a unique numerical identification, the amount of blood collected, expiration date, recommended storage temperature, blood type, appropriate donor identification, additives, and the name and address of the processing facility.[5] Many veterinary blood banks now use a barcode-style system to track product from collection to delivery. The path that the unit has taken from donor to recipient is documented completely, including storage and transport at any intermediate processing or holding facility. In addition to the paper trail, aliquots of the blood components produced are maintained at the principal facility of production to provide the opportunity for testing, if requested.[6] If records are digitalized, paper copies are maintained for the life of the blood product plus 6 months past the expiration date. For example, feline packed red blood cells expire 28 days after collection and separation. Paper copies are maintained for 7 months. If records are solely paper based, copies are held for 5 to 10 years.[3]

ADVANCED STORAGE TECHNIQUES

Unique Solutions to Feline Blood Banking

The drive to produce blood components rather than whole blood for cats has led to the introduction of several novel ways to provide a closed sterile system for use in feline blood banking. Giger[4] describes the use of a sterile docking device and a pediatric quadruple bag system. Using the human pediatric quadruple bag system, 150-ml bags with CPDA-1 are isolated and attached in a sterile manner to 19-gauge butterfly catheters. This provides a sterile closed system that may be used either as a gravity flow collection device or as a vacuum collection system.[4] The sterile docking device used in this technique is cost prohibitive to most veterinary practices. A semiclosed sterile system with onsite addition of CPDA-1 through an injection port has been designed by commercial blood bankers (Figure 57-1). Use of this system has provided a cost-effective means to collect feline blood by syringe or gravity flow and minimize the risk of external bacterial contamination of the blood product. Both systems use polyolefin or polyvinyl chloride as a base. Packaging in plastic allows for the sterile separation from whole blood to components. Glass is not considered a safe medium for blood storage because of its breakability and its inability to accommodate sterile component processing.

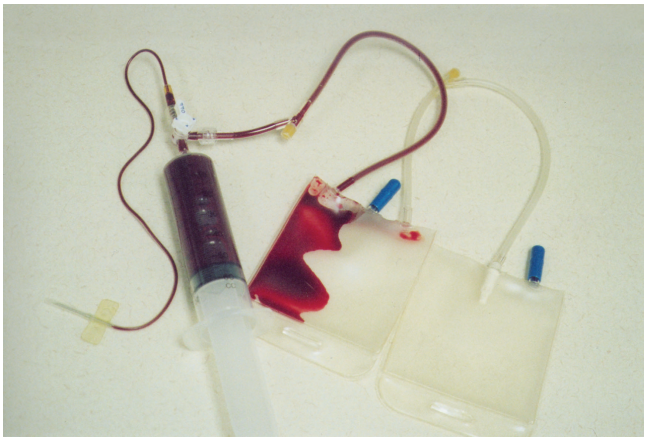

Figure 57-1. This semiclosed system produced by the Animal Blood Bank (Dixon, CA) has been useful in providing a cost-effective means of feline blood component collection.

Storage of product often is not considered a high priority by most practitioners, but when performed incorrectly, the recipient is placed at great risk for non–immune-related transfusion reaction.[7] Temperature, packaging, and appropriate handling during holding and transport periods are very important when trying to avoid storage lesion in blood. Storage lesion is defined as damage to the blood product during its "out-of-body" experience. Indications of storage lesion may include hemolysis, increased or decreased pH, increased ammonia, and/or increased electrolytes. See Table 57-1 for details regarding proper storage of common feline blood components.[8,9] Records of daily temperature are maintained for each storage device. Records also should document mode of transport and condition of the product before and after transport. Documented variations from standard operating procedure exclude the product from normal use. The end user should be made aware of any variation from standard to allow appropriate modifications of product use.

INFECTIOUS DISEASE SCREENING

Perhaps the hardest area of compliance for safety involves the determination of infectious disease screening for donors. A recent workgroup for the American College of Veterinary Internal Medicine prepared a consensus statement on infectious disease screening.[10] Infectious diseases were categorized by

Table 57-1 | **Storage and Transport Recommendations for Common Feline Components**

COMPONENT	STORAGE	TRANSPORT	EXPIRATION	ADDITIONAL CRITERIA
Fresh whole blood	1° to 6°C unless platelet activity is desired 25°C if platelet activity is desired	1-10°C 25°C	28 days 4 hours	Open syringe collections should not be stored for more than 24 hours
Packed red blood cells (pRBC)	1° to 6°C	1° to 10°C	28 days 35-42 days if red blood cell nutrient solution added	
Fresh frozen plasma	<–18° C to –65°C	Maintain frozen state	1 year from collection date	Additional storage as frozen plasma after expiration
Frozen plasma	<–18° C to –65°C	Maintain frozen state	5 years from collection date	

capability for infection through blood products, vector status, and clinical severity of infectious state. The following recommendations were made for cats. Feline leukemia virus and feline immunodeficiency virus status should be evaluated by standard ELISA techniques, detecting antigen and antibody respectively. Evaluation for feline coronavirus is not recommended, because of the lack of correlation between antibody level and disease status. *Mycoplasma haemofelis* and *Mycoplasma haemominutum* are evaluated by microscopic slide evaluation and polymerase chain reaction (see Chapter 63). *Bartonella henselae* infection status is evaluated by antibody titer, blood culture, and/or polymerase chain reaction[11] (see Chapter 4).

Additional vector-borne diseases such as cytauxzoonosis, ehrlichiosis, and anaplasmosis may be added to this testing protocol, depending on the regional location of the donor. The continuing struggle for blood product safety involves the testing interval of the individual. Ideally, from a safety perspective, each unit should be tested for the pathogens listed above in addition to routine bacterial contamination. However, testing at this level increases the cost of the end product greatly. The ACVIM workgroup concluded that, although not ideal, testing should be performed on the donor annually or more frequently if indicated by a change in history or health status.[10]

AVOIDING TRANSFUSION REACTION

The final aspect of safety involves avoiding transfusion reaction in the recipient. Transfusion reaction often is divided into two distinct categories: non–immune-related and immune-related. Both types of transfusion reaction are demonstrated in the recipient in the same way. Mildly affected recipients show hyperemia, dyspnea, hyperthermia, tachycardia, emesis, and urticaria. More severely affected individuals may demonstrate signs of secondary infection, hemolysis, anemia, thrombocytopenia, or even death. Non–immune-related transfusion reactions are caused by circulatory overload, hemolysis resulting from storage lesion, bacterial contamination, hypothermia, and hypocalcemia. Rarely, pulmonary thromboembolism may occur post-transfusion as a non–immune-related reaction. Immune-related transfusion reactions are caused by hemolysis resulting from erythrocyte incompatibility, fever, and chill secondary to lymphocyte transfer, allergy, or anaphylaxis to donor proteins, and/or lymphocyte antigen incompatibility.

Transfusion therapy is performed optimally by selection of the most appropriate blood component and administration of that component in the manner most likely to avoid transfusion reaction. Whole blood, although often a simple and readily available source, may not be the best choice for the transfusion recipient. Component therapy provides an efficient way to supply oxygen-carrying capacity, primary and secondary coagulation capability, and/or oncotic proteins to a critical patient, while it minimizes infectious disease exposure and immune-related reactions. Quality control of components through use of standard operating procedures, the use of modern plastic storage systems, and infectious disease screening further lowers the risk for non-immune reactions. Screening of the donor and recipient for erythrocyte antigens and cross-matching minimizes the risk for immune-related transfusion reaction.

The expansion of transfusion product availability has led to the increased use of blood and blood components in the feline patient. Safety of the blood supply is promoted by careful donor evaluation, thorough record keeping, advanced storage techniques, and avoidance of transfusion reactions. Adherence to the general guidelines discussed in this chapter promotes a safe blood supply capable of enhancing the lives of feline patients with minimal risk.

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Chapter 58

Thromboembolic Disease: Diagnosis and Treatment

Stephanie A. Smith

Normal hemostasis constitutes a delicate balance between procoagulant and anticoagulant responses, with the goals of prevention of blood loss and maintenance of flow within the vascular system. A variety of disorders can tip the balance toward excessive activation of primary and secondary hemostatic mechanisms, which results in inappropriate clot formation. Thrombosis is the formation of a blood clot within the heart or blood vessels, whereas thromboembolism describes a thrombus that has moved from its formation site through the vasculature to become lodged because of the progressive narrowing of the vascular lumen.

Arterial thromboembolism (ATE) was first described in a cat three quarters of a century ago.[1] Since that time, multiple reports have characterized further this devastating clinical presentation in cats. A recent study indicated that ATE was diagnosed in one of 175 feline admissions to a veterinary teaching hospital.[2] Although the diagnosis of ATE in cats is relatively straightforward in those presenting with typical clinical signs, our understanding of the circumstances leading to thrombus formation and our ability to improve the outcome in these patients are still limited.

Pulmonary thromboembolism (PTE) appears to be less common than ATE in cats; two necropsy surveys and some individual case reports have been published. Reports of large numbers of cats with PTE have been limited to necropsy surveys because of lack of clinical suspicion for development of PTE and the challenge of antemortem diagnosis of PTE even for those cats in which PTE is suspected. The prevalence of necropsy-identified PTE was one in 1764 feline admissions in one study,[3] but this figure probably underestimates the true prevalence for several reasons. Thrombi may lyse postmortem,[4] so the diagnosis will be missed if the necropsy is not performed immediately after death, and patients experiencing nonfatal PTE will not be included in any necropsy survey. Regardless of the exact prevalence of thromboembolism in cats, thrombus development has the potential to be a devastating event for any cat in which it occurs.

PATHOPHYSIOLOGY OF THROMBUS FORMATION

The exact underlying mechanism leading to formation of inappropriate thrombi in cats is unclear, and multiple mechanisms likely play a role in most patients. Thrombus formation may result from alterations in the endothelial surface, blood flow, and/or composition of the blood (Table 58-1). This concept, known as Virchow's triad, provides the cornerstone for understanding the pathophysiological factors that predispose patients to develop inappropriate thrombosis (Figure 58-1).

Changes in the Endothelial Surface

The potential for thrombus formation is enhanced whenever the vessel wall is inflamed or injured. Disruption of the endothelial surface exposes subendothelial collagen, von Willebrand's factor, and tissue factor, all of which may initiate clot formation (Figure 58-2). The vessel wall may be damaged by inflammatory diseases causing local or systemic vasculitis, penetration of the vascular wall by foreign material, and invasion of the vascular wall by neoplasia.

Placement of indwelling catheters results in local injury to the vascular wall. Catheter-associated thrombosis has not been investigated thoroughly in cats, but 20 per cent of cats undergoing hemodialysis had right atrial thrombosis on echocardiographic examination, and 72 per cent of cats with PTE in one study had had an indwelling catheter placed.[5] Catheter-associated thrombosis in cats has been used as an experimental model for the study of antithrombotic therapy.[6] Because most hospitalized feline patients experience indwelling catheter

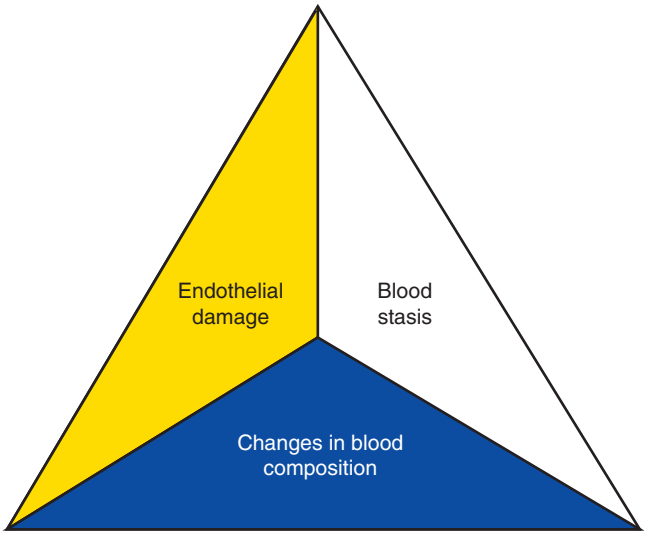

Figure 58-1. Virchow's triad describes the multiple factors that may lead to development of inappropriate thrombosis.

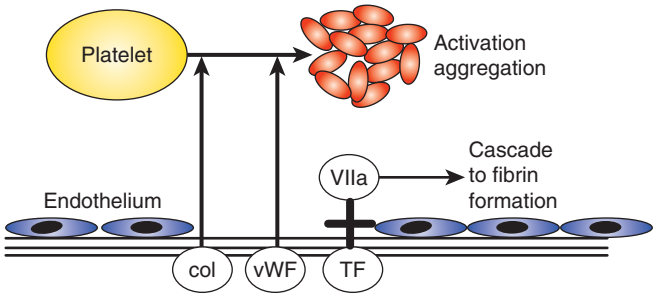

Figure 58-2. The vessel wall may be damaged by inflammatory diseases causing local or systemic vasculitis, penetration of the vascular wall by foreign material, or invasion of the vascular wall by neoplasia. Disruption of the endothelial surface exposes subendothelial collagen (col) and von Willebrand's factor (vWF), both of which can bind to platelet receptors, resulting in platelet activation and ultimately aggregation to form a platelet plug. Endothelial injury also can expose tissue factor (TF), which is the primary initiator of secondary hemostasis. The coagulation cascade, once instigated by binding of activated factor VII (FVIIa), ultimately results in formation of a fibrin clot.

Table 58-1 | **Disease Processes Associated with Thrombus Formation in Cats**

CHANGES IN THE ENDOTHELIAL SURFACE/ DAMAGE TO THE VESSEL WALL
Vasculitis
Feline infectious peritonitis
Immune-mediated vasculitis
Bacterial infection of catheters
Caustic or hypertonic drug injection
Pancreatitis
Sepsis
Heartworm disease
Penetration of the vessel
Indwelling catheter
Migrating foreign body
Invasion of the vessel
Neoplasia
BLOOD STASIS
Cardiac enlargement
Vascular aneurysm
Obstruction
Ligation
Neoplasia
Embolus
Surgical placement of foreign material
CHANGES IN BLOOD COMPOSITION (THROMBOPHILIA)
Thrombocytosis
Platelet hyperaggregability
Cardiac disease?
Coagulation inhibitor deficiency
Protein-losing nephropathy or enteropathy
Consumptive coagulopathy (DIC)
Increased coagulation factor activity
Neoplasia
Massive trauma
Systemic inflammatory response syndrome
Immune-mediated hemolytic anemia
Pancreatitis
Sepsis
Other infectious and inflammatory diseases
Mechanism not clearly defined
Hyperadrenocorticism
Previous or current hyperthyroidism?
Factor XII deficiency?

placement, the potential risk, if any, for thrombosis associated with an indwelling catheter is unclear.

Changes in the endocardial surface may develop in cats with cardiac disease. A necropsy study of cats with cardiac disease described cases in which the endothelium was damaged, and cellular debris and fibrin had adhered to the subendothelial tissues.[7] Neoplastic invasion of the vascular wall also may cause endothelial injury and initiate local thrombus formation.[8]

Blood Stasis

Peripheral vascular stasis may occur because of compression or occlusion of a vessel by a tumor or placement of vascular access devices. However, in these circumstances endothelial injury also is a factor in thrombus development. Blood stasis also may occur secondary to left atrial enlargement, as is common in cats with cardiac disease. The majority of cats presenting for ATE with concurrent cardiac disease have some degree of left atrial enlargement[2,9,10] and presumably secondary blood stasis in the left atrium. In contrast, although a variety of canine cardiac diseases are associated with severe left atrial enlargement, ATE is extremely rare in dogs, which suggests that stasis by itself is not a major risk factor for thrombosis in this species.

Peak flow velocity in the left atrial appendage was lower in cats with cardiomyopathy (0.31 m/sec) than in normal cats (0.46 m/sec), and even lower in cats with left atrial thrombi (0.14 m/sec), which suggests that lower flow is associated with development of ATE.[11] If stasis is a major contributing factor, the more severe the atrial enlargement, the more likely that a thrombus will form. In one study, cats with hypertrophic cardiomyopathy (HCM) and ATE did have significantly larger left atria than those presenting with congestive heart failure (CHF) without ATE, and cats that developed ATE after the initial examination also had significantly larger left atria than cats that did not develop ATE.[12] However, more severe left atrial

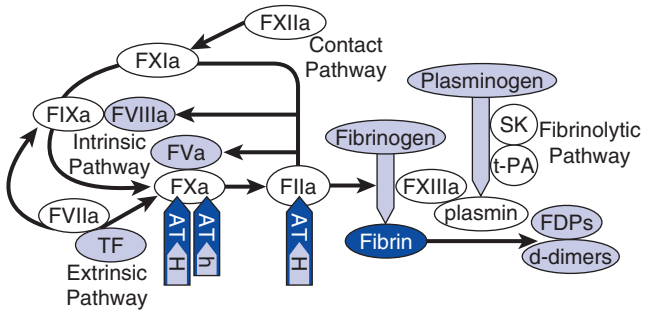

Figure 58-3. Simplified coagulation and fibrinolysis cascades. The coagulation pathway consists of the extrinsic pathway, intrinsic pathway, and common pathway. For simplicity, factor zymogens and the protein C pathway have been omitted. The extrinsic pathway is the physiologically relevant initiator of coagulation. The intrinsic pathway functions primarily to amplify generation of thrombin (FIIa). The contact pathway is not a relevant source of thrombin generation in vivo, but is the primary source in vitro when blood is placed in glass tubes and during the activated partial thromboplastin time. Activity of the inhibitor antithrombin (AT) is enhanced markedly when unfractionated heparin (H) or low-molecular-weight heparin (h) is administered, the latter of which is unable to impact AT activity against thrombin. The fibrinolysis pathway consists of the cleavage of fibrin by plasmin to its various degradation products, including D-dimers. Plasminogen is activated to the enzyme plasmin by several enzymes, including tissue plasminogen activator (t-PA) and streptokinase (SK), both of which are available for therapeutic use.

enlargement occurs with more severe cardiac disease. Consequently, it is not possible to differentiate the effects of stasis in the left atrium from other as yet unknown effects on coagulation or endothelial function because of severe cardiac disease in cats.

Blood Composition

Changes in blood composition also may play a role in development of inappropriate thrombi (Figure 58-3). A hypercoagulable state, or thrombophilia, may be either acquired or hereditary in origin. A coagulation protein or platelet defect is identified in more than 50 per cent of human beings with thrombosis.[13] Abnormalities in procoagulant and anticoagulant proteins that lead to hypercoagulability unfortunately have not been investigated extensively in cats.

Acquired Thrombophilia

Acquired thrombophilia may occur secondary to disease states such as cardiac disease, protein-losing disorders, endocrinopathies, or neoplasia. In one study that compared 11 cats with cardiac disease (9 secondary to hyperthyroidism) to normal cats, antithrombin (AT) was relatively increased and plasminogen activity was mildly decreased. These cats also had abnormal platelet aggregation with decreased responsiveness to adenosine diphosphate (ADP) and increased responsiveness to collagen.[14] The described changes could have been due to hyperthyroidism rather than cardiac disease. Note also that, in theory, increased AT activity should result in a *decrease* in thrombogenicity. In another study, plasma homocysteine levels were not different between normal cats, cats with cardiomyopathy, and cats with cardiomyopathy and ATE.[15] In one study, platelets from cats with cardiomyopathy required less ADP to induce aggregation than platelets from normal cats, which indicates that the platelets were hyperaggregable in cats with cardiac disease.[16]

Protein-losing disorders may cause an acquired thrombophilia resulting from deficiency in the important coagulation inhibitors AT, protein C, and the cofactor protein S. Because these proteins are somewhat smaller than albumin, any disorder causing clinically relevant loss of albumin generally results in concomitant loss of the coagulation inhibitors. Thrombosis secondary to protein-losing nephropathy or enteropathy is well documented in human beings and dogs, and PTE has been described in cats with protein-losing nephropathy.[5]

Endocrinopathies also have the potential to cause hypercoagulability in cats. As noted previously, cardiac disease resulting primarily from hyperthyroidism was associated with a possible defect in fibrinolysis and platelet hyperaggregability.[14] Another report described ATE in multiple cats with current untreated or previously treated hyperthyroidism (euthyroid at the time of the ATE) in the absence of echocardiographically identifiable cardiac disease.[2] Hyperadrenocorticism is associated with a well-documented hypercoagulability in dogs leading to the development of PTE.[17] Although Cushing's syndrome is rare in cats, reports exist of thrombosis in association with spontaneous hyperadrenocorticism.[18,19]

Thrombus development secondary to neoplasia is a frequently reported phenomenon in human beings and animals. Some tumors express tissue factor and other procoagulant proteins, resulting in intravascular activation of coagulation independent of exposure of extravascular tissue factor. In patients with neoplasia, deficiency of coagulation inhibitors may develop secondary to excessive consumption, hepatic dysfunction, and exposure to chemotherapeutic agents.[20] Fibrinolysis is defective in patients with cancer, and paraneoplastic thrombocytosis may develop.[21]

Inherited Thrombophilia

Despite the high prevalence of documented inherited thrombophilia in human beings, a specific inherited form of genetic tendency for thrombosis has not been described as yet in a cat. Any genetic abnormality causing thrombophilia would manifest as a breed predisposition for thrombosis. In retrospective studies describing a total of 195 cases of ATE and 46 cases of PTE in cats, breed comparison to hospital population was not reported, but the majority of affected cats were of mixed breeding. Affected pure breeds included Abyssinian, Birman, Himalayan, Persian, Siamese, Manx, and Maine Coon.[3,5,9,10,22] In a retrospective study of 127 cats with ATE in which breed representation was compared with the hospital population, the latter three breeds also were reported, but at rates comparable to the hospital population. Abyssinian, Birman, and Ragdoll were overrepresented as compared with the hospital population.[2] This overrepresentation could be explained by either an increased genetic risk for cardiac disease or an unrelated genetic risk for ATE. In a comparison population of 271 cats with cardiac disease presenting initially for CHF rather than ATE, Birman and Ragdoll cats were similarly overrepresented, but Abyssinian cats were underrepresented.[2] Therefore Birman and Ragdoll cats likely have a genetic predisposition for cardiac disease rather than ATE. Abyssinian cats may or may not have an as yet undetermined hereditary thrombophilia.

A single family of cats with HCM has been described in which 75 per cent of cats developed ATE.[23] These cats all may

have developed ATE because they exhibited a particularly severe form of HCM. But in human beings, families with a high density of individuals affected by thrombosis usually have an identifiable genetic thrombophilic risk factor.[24] Consequently, it is possible that this family of cats inherited a predisposition for hypercoagulability.

Some studies indicate that Hageman trait, a hereditary deficiency of coagulation factor XII (FXII) activity, is associated with an increased risk for deep venous thrombosis (DVT) in human beings.[25] FXII deficiency is a well-described abnormality in cats that results in prolongation of the activated partial thromboplastin time (APTT) without a bleeding tendency.[26] Whether or not FXII deficiency causes thrombophilia in cats has not been evaluated.

The concept that some cats may have an inherited hypercoagulability is supported additionally by occasional reports of feline thromboembolism, in which aggressive diagnostic tests fail to identify a specific underlying disease.[2,3] An underlying genetic abnormality of coagulation could explain this apparent "idiopathic" thrombosis. Furthermore, in human beings and cats, a single episode of thrombosis increases the risk of developing a future thrombus markedly.[13] In human beings, the reason for this increased risk is that those developing a thrombus usually have an identifiable inherited or acquired risk factor.

Specific Risk Factors for Development of Thrombosis or Thromboembolism

The distribution of associated diseases in cats presenting with ATE from one study[2] and cats diagnosed postmortem with PTE from two other studies[3,5] is shown in Figure 58-4.

All forms of cardiomyopathy appear associated with an increased risk for ATE. No studies have reported the relative risk of ATE with specific cardiac diseases as compared with other disease, but ATE has been reported to occur in 12 per cent,[27] 13 per cent,[28] and 28 per cent[12] of clinical patients with HCM, and in 41 per cent in a necropsy survey.[29] Several studies have reported a gender predilection for ATE in male cats,[9,10,22] but this appears to be due primarily to the greater predisposition of male cats to develop HCM.[2] Although previous recommendations sometimes indicated that a left atrial dimension in systole (LADs) measurement of greater than 2.0 cm constitutes significant risk for development of a thrombus, recent reports noted that approximately half of ATE patients had LADs less than 2.0 cm, which indicates that any degree of enlargement may be associated with ATE in cats.[2,12]

Cardiac disease also has been described in association with PTE.[3,5] Because pulmonary thrombi may be due to embolism from thrombi that formed in the right side of the heart, they are more likely to be associated theoretically with cardiac diseases in which right-sided cardiac abnormalities occur (e.g., such as dilative cardiomyopathy or tricuspid valvular disease) than with predominantly left-sided diseases.

Neoplasia,[21] particularly pulmonary carcinoma,[2,3,9,10] also presents a risk factor for development of thromboembolism in cats. Pulmonary tumors generally have ready access to the pulmonary vasculature, with the potential for initiation of local thrombus formation or tumor invasion leading to neoplasia within the vessel and consequent tumor embolism. Thrombus formation or tumor detachment in the pulmonary arterial system may result in embolism to the pulmonary vasculature via the right heart, whereas thrombus formation or tumor detachment in the pulmonary venous system may result in embolism to a systemic artery via the left heart. Ischemia resulting from tumor embolus as a cause of arterial occlusion is indistinguishable clinically from thromboembolus and should be

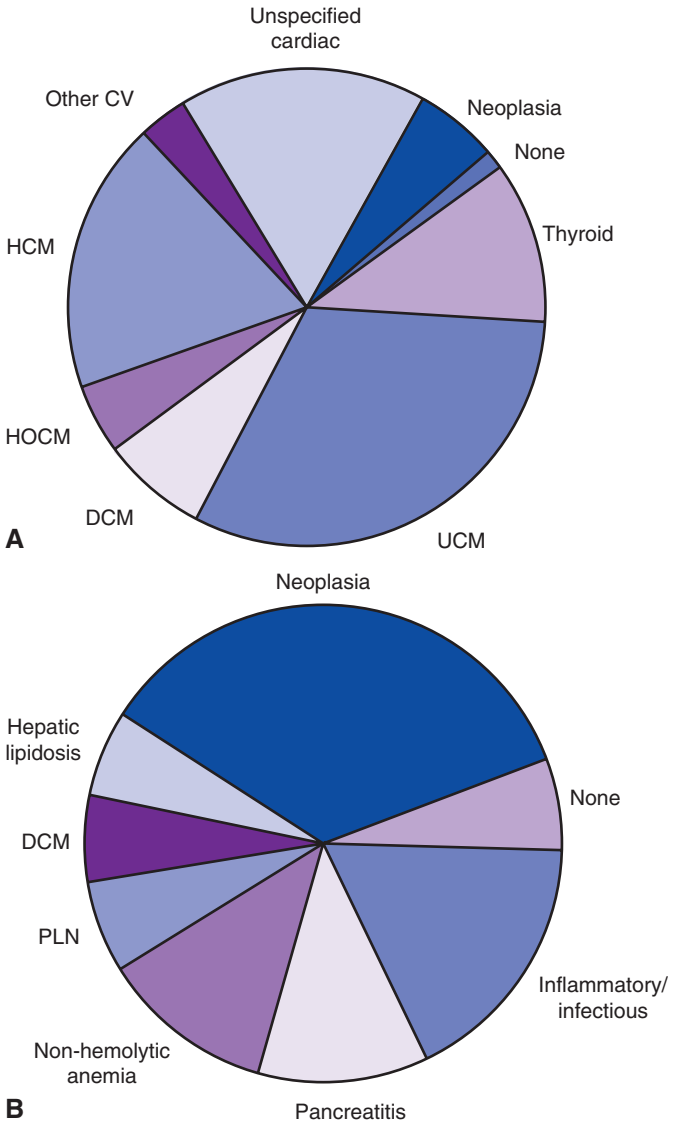

Figure 58-4. Disorders in 108 cats presenting with arterial thromboembolism in which diagnostic tests were performed[2] **(A),** and 29 cats diagnosed with pulmonary thromboembolism on necropsy examination[3] **(B).** "Unspecified cardiac" indicates cats in which necropsy identified cardiac disease, but no specific diagnosis was made because antemortem echocardiography was not performed. "Thyroid" includes cats with newly diagnosed and previously treated hyperthyroidism. Inflammatory/infectious diseases included encephalitis, feline infectious peritonitis, and bacterial pneumonia. "None" indicates that no disease was identified on echocardiography or other diagnostic tests. *DCM,* dilated cardiomyopathy; *HCM,* hypertrophic cardiomyopathy; *HOCM,* hypertrophic obstructive cardiomyopathy; *UCM,* unclassified cardiomyopathy; *PLN,* protein-losing nephropathy. An additional report described pulmonary thromboembolism in 29 cats secondary to similar disease processes, but 47 per cent had multiple diseases preventing this type of diagrammatic representation. Underlying conditions described in that report were cardiac disease (12), neoplasia (10), disseminated intravascular coagulation (5), protein-losing nephropathy (4), protein-losing enteropathy (4), immune-mediated hemolytic anemia (2), and sepsis (2).[5]

considered in cats with concurrent pulmonary masses presenting with typical signs of ATE.[30]

ATE in cats with thyroid disease may occur secondary to thyrotoxic cardiomyopathy[9] but also has been reported in previously hyperthyroid cats that were euthyroid at the time of the ATE episode and had echocardiographically normal hearts.[2] Thyroid disease consequently may pose a risk factor for ATE that is independent of the cardiac effects of hyperthyroidism.

Inflammatory and infectious diseases that upregulate systemic activation of coagulation cause loss of endothelial anticoagulant properties and may result in either microvascular thrombosis (generally occurring as disseminated intravascular coagulation) or probable thrombosis leading to PTE. Specific systemic inflammatory diseases reported in cats with PTE include pancreatitis, immune-mediated hemolytic anemia, feline infectious peritonitis, and bacterial infection or sepsis.[3,5]

CLINICAL PRESENTATION

The clinical effects of thrombosis or thromboembolism are dependent on the location of the thrombus. Thrombi that form within the heart may affect cardiac filling adversely or cause obstruction of outflow. Thrombi that form within the arterial vasculature, or those from the left side of the heart that embolize to the arterial vasculature, cause obstruction of arterial flow, resulting in ischemia of downstream tissues. Thrombi that form within the venous system cause interference with venous drainage of tissues, resulting in edema or fluid accumulation in body cavities. Venous thrombi or those that form in the right side of the heart may embolize to a pulmonary artery, which leads to ventilation/perfusion mismatch, prevents oxygen uptake, and causes hypoxemia. The majority of feline patients presenting with thrombotic disease are affected by cardiac thrombi that have embolized to a major artery. Central venous thrombosis and pulmonary thromboembolism are rare in cats.

Arterial Thromboembolism

The clinical signs associated with ATE are referable to acute ischemia of the tissue supplied by the occluded artery. The location of the embolus is dependent on the size of the embolus and the anatomy of the vascular tree. Because most thrombi that form in the atria reach a reasonably large size before dislodging, the majority of thromboemboli lodge in the aorta or one of its major branches, affecting blood supply to one or more of the limbs. If the embolus settles in the "saddle" location at the distal aortic trifurcation, both rear limbs will be affected. This is the most common presentation (71 per cent). Smaller emboli may travel into more distal arteries and impact arterial flow to only one limb. Unilateral rear limb thromboembolism is much less common (14 per cent) and may affect either limb. Single forelimbs also may be affected as a result of obstruction of a brachial artery (12 per cent) with right (7 per cent) and left (5 per cent) almost equally common. In a few cases, multiple sites are affected (2 per cent). Rarely, nonappendicular sites may be affected, including a cerebral artery, renal artery, or mesenteric artery.[2]

Clinical effects of occlusion of limb perfusion include lameness, plegia or paralysis, and pain. Nail beds and pads may appear pale to cyanotic, depending on the degree of ischemia, and the limb may be cool as compared with nonaffected limbs. Loss of motor function is common (66 per cent), especially when both rear limbs are affected.[2]

Pulmonary Thromboembolism

The clinical signs associated with PTE are referable to ventilation/perfusion mismatch. As for manifestations of many serious illnesses in cats, clinical signs may be nonpecific. Lethargy, depression, tachypnea, and/or dyspnea may be noted.[5] Because these findings are nonspecific and often ascribed to the underlying illness that has predisposed the cat to develop PTE, clinical suspicion for this complication often is low.

Systemic Effects of Thromboembolism

Occlusion of a major vascular bed, whether arterial, venous, or pulmonary, causes maldistribution of blood flow by preventing perfusion of, or venous return from, the affected vasculature. Furthermore, release of vasoactive substances results in dysregulation of vessel tone, which affects perfusion to sites not affected by the embolus. This leads to the potential for maldistributive shock and circulatory collapse. Cats with underlying cardiac disease also have the potential to develop cardiogenic shock. Cats with ATE also may develop reperfusion injury associated with profound tissue ischemia. Reperfusion injury leads to electrolyte dyscrasias, acidosis, and azotemia.[2,10]

A variety of aspects of the clinical presentation of cats with thromboembolism are attributable to shock. Clinical manifestations of inadequate systemic perfusion include rectal hypothermia, even when the distal aorta is not the obstructed site, and azotemia with an elevated BUN/creatinine ratio.[2] The majority of cats with ATE are tachypneic or apparently dyspneic, even in the absence of CHF.[2] This abnormal respiratory pattern may be a manifestation of the obvious and considerable pain experienced by these patients. Affected cats may demonstrate excitement, frenzy, vocalization, rolling, and panting.

True dyspnea with inadequate gas exchange resulting from pulmonary abnormalities may occur with either ATE or PTE. If the affected cat has underlying cardiac disease, CHF may develop either before, in conjunction with, or subsequent to the embolic event. Cor pulmonale may result from the acute increase in right ventricular afterload in cats with PTE.[31] Congestive heart failure resulting in pulmonary edema or pleural effusion limits pulmonary gas exchange. Respiratory compromise leading to hypoxemia also may be present in cats without cardiac disease resulting from pulmonary masses, noncardiogenic edema secondary to PTE, or because of the lack of pulmonary perfusion directly attributable to the obstructed pulmonary artery.

DEFINITIVE DIAGNOSIS

Appendicular Arterial Thromboembolism

Although the diagnosis of limb ischemia generally is straightforward in cats that present with the classic five Ps (pulselessness, pain, pallor, paresis, poikilothermia), confirming appendicular ATE in other cats may be more challenging (Table 58-2). Lack of a palpable pulse itself is not diagnostic for ATE. Femoral pulses often are not easily palpable in obese or uncooperative cats, regardless of the level of flow. Poor quality or absent pulses occur associated with systemic hypotension;

Table 58-2 | **Diagnostic Findings Supportive of Arterial Thromboembolism as the Cause of Acute Limb Paresis or Paralysis**

Lack of identifiable pulse in the affected limb using Doppler
Concurrent evidence of cardiac disease
Elevations of enzymes released from damaged muscle (AST, CK)
Venous glucose from affected limb markedly less than central venous glucose
Ultrasonographic identification of intravascular thrombus
Loss of normal perfusion on scintigraphic perfusion scan

Table 58-3 | **Diagnostic Findings Supportive of Pulmonary Thromboembolism as the Cause of Respiratory Abnormalities**

Hypoxemia, especially if characterized by an increased alveolar-arterial gradient
Echocardiographic evidence of right ventricular pressure overload or pulmonary hypertension
Unremarkable thoracic radiographs in the face of significant respiratory compromise
Oligemia or truncated pulmonary arteries on thoracic radiographs
Ventilation/perfusion mismatch on scintigraphic scan
Elevated D-dimers?

therefore these signs are not specific for obstructed arterial flow. For cats presenting with forelimb signs, pulse identification often is challenging even in cats with normal arterial flow.

Cats with partially obstructed brachial or femoral arteries present with more subtle signs. Differential diagnoses for acute loss of limb function should include spinal cord disease (intervertebral disc disease, spinal neoplasia, embolus, trauma, foreign body), peripheral neuropathies (especially diabetic neuropathy), and acute abnormalities in brain function (embolism, trauma, shock, neuroglycopenic crisis, and toxicity).

The majority of cats with ATE have underlying cardiac disease.[2] Support for ATE as the etiology for loss of limb function may be identified consequently by careful physical examination when a murmur, gallop, or arrhythmia is detected. However, because many cats with cardiac disease do not have such findings, the absence of auscultable cardiac abnormalities does not exclude ATE. Simple diagnostic evaluations can lend additional support to a diagnosis of appendicular ATE. In cats with plegia and nonpalpable pulses, evaluation of arterial flow by Doppler is extremely useful. ATE is probable if arterial flow cannot be detected. However, because appendicular arteries may be partially occluded, positive identification of arterial flow does not exclude ATE as the cause of limb paresis. Because of the muscle ischemia, cats with ATE generally have elevations of serum enzymes released from damaged muscle cells. Increased aspartate aminotransferase has been reported in 83 to 99 per cent of cats with ATE.[2,9,10] Creatine kinase, although reported in relatively few cases, also is frequently elevated (80 to 100 per cent), often to a marked degree.[2,22] Support for ATE also may be obtained by comparison of a venous blood sample acquired from the affected limb to that acquired from a central vein. Local venous glucose (50 ± 25 mg/dL) was significantly lower than central venous glucose (182 ± 89 mg/dL) in cats with appendicular ATE, and in every case, the local venous glucose was markedly lower than the central venous glucose.[32] Additionally, local venous lactate (10.7 ± 2.7 mmol/L) was significantly higher than central venous lactate (2.1 ± 0.8 mmol/L).[32]

The specificity of serum muscle enzyme elevations, decreased local glucose concentration, and increased local lactate concentration as a diagnostic tool for distinguishing ATE from other causes of subtle limb signs in cats has not been evaluated critically. However, the high prevalence of muscle enzyme elevations in cats with ATE suggests these are sensitive discriminatory tests. Consequently, ATE is unlikely to be the cause of limb signs in cats in which these serum chemistry abnormalities are absent.

More expensive and invasive diagnostic tests may be indicated in some cases to confirm a diagnosis of ATE. Radiography, ultrasonography, angiography, and nuclear scintigraphy

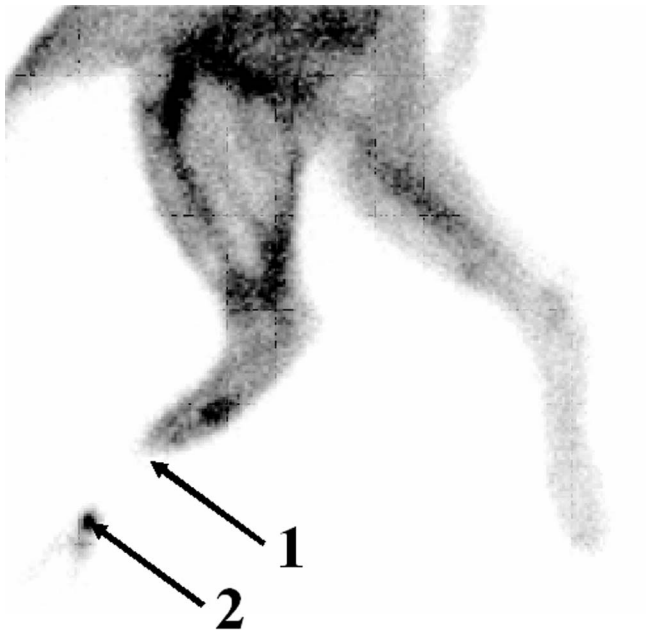

Figure 58-5. Lateral image of the pelvic limbs of a cat with hypertrophic cardiomyopathy and a distal aortic thrombus causing acute bilateral rear limb paralysis. The image was obtained after intravenous injection of 2.4 mCi $^{99m}TCO^{-}_{4}$. At the time of the perfusion imaging, the patient had recovered complete motor function in the right rear limb, but the left rear limb distal to the mid metatarsus *(1)* had failed to regain function. The radioactive marker dot *(2)* indicates the location of the tip of the left foot.

can be used to evaluate the obstructed site further. These imaging modalities may provide additional information, particularly when other diagnostics have failed to identify an underlying etiology for ischemia. In cases in which the etiology of the obstruction is local rather than embolic (i.e., neoplastic invasion, foreign body, vasculitis), these imaging techniques may be especially useful for evaluation of the vessel wall at the site of the obstruction. Nuclear scintigraphic perfusion scans also may provide prognostic information regarding the likelihood of recovery of limb perfusion[33] (Figure 58-5).

Pulmonary Thromboembolism

The premortem diagnosis of PTE is extremely challenging. PTE should be considered as a differential diagnosis in all feline patients with acute or insidious onset of respiratory distress, especially when the patient already has been diagnosed with a disease process known to be associated with PTE (Table 58-3).

Radiographic evaluation of the thorax may or may not be of benefit. The logical expected finding of regional oligemia is the exception rather than the rule and difficult for the less experienced radiographer to identify. Thoracic radiographic findings in cats with PTE may include edema and pleural effusion, which makes PTE difficult to distinguish from other causes of pulmonary disease. Pulmonary masses and secondary atelectasis also may be present.[3,5] Thoracic radiographs may even be unremarkable, although when a dyspneic, hypoxemic patient has unremarkable thoracic radiographs, the most likely diagnosis is PTE. Evidence of right ventricular pressure overload or pulmonary hypertension on echocardiographic examination also is supportive of a diagnosis of PTE, but lack of such findings does not rule out PTE as the cause of respiratory signs.[34,35]

Evaluation of gas exchange is indicated for any dyspneic patient, but acquiring the appropriate diagnostic information often is difficult in a cat with respiratory compromise. Noninvasive pulse oximetry indicates below-normal hemoglobin saturation. Arterial blood gases often are difficult to acquire in cats, but hypoxemia characterized by an increased alveolar-arterial gradient supports a diagnosis of PTE. Hypoxemia is not a specific finding in human beings and dogs.[35] Although the majority of reported cases of necropsy-confirmed canine PTE had elevated alveolar-arterial gradients,[34] 20 per cent of human patients with proven PTE have a normal alveolar-arterial gradient.[35]

The gold standard for diagnosis of PTE in human beings is nuclear scintigraphic ventilation/perfusion imaging.[35] Although this diagnostic test is available for feline patients, its use is limited primarily to academic centers (Figure 58-6). The primary disadvantage of nuclear scintigraphy is the need for isolation of the patient because of regulations regarding handling of radioactivity. Because most patients with PTE are critically ill, isolation and minimal hands-on care generally are not reasonable options.

Spiral CT scans are replacing nuclear scintigraphy gradually in human medicine for diagnosis of PTE because of the dangers of radionucleotide use.[35] Although the test itself is noninvasive, most feline patients require heavy sedation or anesthesia during a CT scan. Cats with PTE generally represent a significant anesthetic challenge, so use of the CT technology for diagnosis of PTE may be limited.

Figure 58-6. Dorsoventral image of the thoracic cavity of a cat with anaplastic carcinoma and a right pulmonary artery thromboembolism. The image was obtained after intravenous injection of 2.4 mCi $^{99m}TCO^{-}_{4}$. No indication exists of any perfusion to the entire right lung. A ventilation scan *(not shown)* performed immediately before the perfusion scan indicated uniform ventilation of both the right and left lung.

Coagulation Testing for Thromboembolism

Routine coagulation tests generally are unremarkable for cats presenting with thromboembolism.[36] In cats with ATE in which coagulation panels were performed before therapy, 75 per cent were within reference range.[10] Markers of active fibrinolysis such as D-dimers and fibrin(ogen) degradation products may be elevated,[37] especially after administration of thrombolytic therapy.[10] In human beings, a low D-dimer result is a specific finding to rule out the presence of PTE,[35] and D-dimers generally are elevated in dogs with thromboembolism,[38] but the usefulness of this test for diagnosis of thromboembolism in cats has not been evaluated.

TREATMENT

Management during the initial crisis primarily should address systemic perfusion issues, correct hypoxemia, and provide analgesia. Of secondary importance is resolution of limb ischemia in ATE, especially because recent reports have suggested that specific efforts aimed at improving limb perfusion in cats with ATE may affect patient survival adversely.[10,39] Prevention of thrombus extension (and the resulting worsening of ischemia) probably is indicated but of unproven efficacy.

Addressing Systemic Perfusion

Improving systemic perfusion probably is the most important goal in managing the acute crisis in patients with thromboembolism. Because these patients often are hypothermic, previous reports have advocated application of heat sources to increase body temperature.[40] However, hypothermia is a manifestation of poor systemic perfusion and shock. External warming may cause peripheral vasodilation, shunt blood away from vital core organs, and consequently *worsen* core perfusion. External warming therefore is not indicated unless hypothermia persists after systemic perfusion has been addressed.

Correcting systemic perfusion is a significant challenge in these patients because the precise pathophysiology of shock is seldom clear. Fluid therapy is indicated for the dehydrated patient and those not in CHF. On the other hand, administering fluids to any patient with cardiac disease must be performed with utmost caution. Positive inotropes may have a role in management of cats with ATE, especially in cases with depressed systolic cardiac function. Clearly, more research is needed to

determine the ideal approach to managing systemic perfusion in cats with thromboembolism.

Administration of acepromazine to decrease anxiety and to improve arterial flow to the ischemic area by its vasodilatory effect has been recommended occasionally.[41,42] No study has evaluated the use of this drug in cats with ATE. Furthermore, this hypotensive drug has the potential to exacerbate shock. The use of acepromazine therefore is not considered appropriate for cats with thromboembolic disease.

Analgesia

The negative effects of pain on patient morbidity and mortality are well documented. Clearly, analgesic therapy is indicated for cats with ATE and may improve some clinical signs. The particular analgesic therapy that best addresses the pain of ATE in cats has not been evaluated. Use of torbutrol, morphine, oxymorphone, and fentanyl has been reported.[2]

Management of Respiratory Compromise

The lack of association between tachypnea and the presence of heart failure in cats with ATE presents a therapeutic challenge. Cats with tachypnea or dyspnea and auscultation findings supportive of cardiac disease or pulmonary edema often are treated empirically with furosemide before diagnostic evaluation; however, these cats may or may not actually have CHF. The volume reduction and/or vasodilation that results from medications used routinely for the treatment of CHF worsens systemic perfusion. Thoracic radiography is indicated before administration of furosemide for any cat with ATE, regardless of respiratory status.[2] Once the presence of CHF is confirmed in cats with underlying cardiac disease, appropriate therapy is not different than that administered to cats presenting with CHF without ATE. Cage rest, oxygen supplementation, thoracocentesis, furosemide, and venodilators should be used as appropriate for the patient (see Chapter 34).

Cage rest in an oxygen-enriched environment is not detrimental to those feline patients that show an abnormal respiratory rate and pattern resulting from stress and pain rather than CHF or pulmonary disease. On the other hand, it is beneficial for patients with hypoxemia resulting from pulmonary edema and may be beneficial in cats with ventilation-perfusion mismatch. Consequently, oxygen supplementation, preferably via an oxygen cage, is indicated for all patients presenting with respiratory signs.

Additional Supportive Measures

Cats with thromboembolism usually are critically ill. Additional supportive measures may include judicious fluid administration to maintain proper hydration (ideally limited to patients *not* in CHF) and nutritional support as indicated.

Thrombolytic Therapy

No controlled clinical trials have evaluated the use of thrombolytic agents in cats with ATE, although several case series have been reported. Between the various available thrombolytic agents, no drug appears superior for lysis of thrombi in human beings.[43] Use of two agents, streptokinase and tissue plasminogen activator, has been described in cats for lysis of ATE but not for PTE.

Tissue Plasminogen Activator

Tissue plasminogen activator (t-PA) is a naturally occurring glycoprotein that catalyzes the conversion of plasminogen to plasmin in the presence of fibrin (see Figure 58-3). Human recombinant t-PA is available for clinical use. As a nonfeline protein, it has the potential to be antigenic. In addition, the drug is extremely costly.

The use of t-PA for the treatment of ATE in cats has been reported in a single study involving six cases. The drug was administered at a dosage of 3.0 to 8.0 mg/kg IV. Perfusion was restored in 64 per cent of the affected limbs. The rate of survival to discharge was 50 per cent. Reported complications were hyperkalemia, acidosis, mild hemorrhage, and fever.[44,45]

Streptokinase

Streptokinase (SK) is a bacterial protein isolated from a human-specific pathogenic streptococcus.[46] When administered systemically, it accelerates activation of fibrin-bound plasminogen to plasmin[47] (see Figure 58-3). SK variants exhibit a limited spectrum of function against mammalian plasminogens, with cleavage action potentially optimal for, or restricted to, plasminogen from the species infected normally by the bacterium producing the streptokinase.[48] As a bacterial protein, it has the potential for antigenicity. The drug also is costly, but much less so than t-PA.

SK has been used successfully to lyse experimentally induced thrombi in normal cats. No adverse effects were noted during the infusion, but the animals were euthanized shortly after the infusion was complete.[49] In a prospective study of eight client-owned cats with ATE (six) and left atrial thrombi (two) evaluating SK as a thrombolytic agent, use of this drug was associated with 100 per cent mortality. Adverse effects included neurological signs, respiratory distress, and electrolyte dyscrasias.[39]

Another study reviewed 46 cats with ATE retrospectively that had been treated with SK. Although arterial pulses and motor function returned in many cases, only 33 per cent survived to be discharged from the hospital. Reported complications were hyperkalemia with metabolic acidosis, and overt hemorrhage (24 per cent).[10] In comparison, in a retrospective study of 83 cats with ATE managed without thrombolytic therapy (all treated with heparin and/or aspirin), 45 per cent survived to be discharged.[2] Overt bleeding was not observed in any of these patients, although two cats (2 per cent) had other evidence of hemorrhage.[2]

In cats with ATE, ischemia of tissues distal to the thrombus often is severe because of the massive amount of limb tissue often affected by the arterial occlusion and the potential delay in presentation of cats with ATE. The frequency of hyperkalemia, acidosis, and death suggests that reperfusion injury is a serious problem in cats treated with thrombolytic agents. In human beings, thrombolytic therapy is indicated in acute appendicular arterial occlusion in patients when associated with profound limb ischemia, *except* when revascularization of the ischemic limb could jeopardize patient survival.[46] Clearly, use

of thrombolytics in cats with ATE has the potential to cause fatal reperfusion injury. The frequency of hemorrhagic complications also is high. Additionally, use of these agents is associated with significant cost. Given these factors, in addition to the lack of evidence for improved outcome in cats treated with thrombolytics compared with cats not treated with thrombolytics, the use of thrombolytic drugs is difficult to justify in cats with ATE.

Anticoagulant Therapy

Anticoagulants are recommended during the acute crisis associated with thromboembolism. The aim of such therapy, at least in theory, is to prevent or reduce additional clot formation and the consequent further reduction in blood flow. Because of a lack of controlled clinical trials, the efficacy of anticoagulant therapy in the treatment of cats with thromboembolism has not been established.

Unfractionated Heparin

Unfractionated heparin (UH) is a heterogeneous mixture of sulfated mucopolysaccharides. It catalyzes the binding of antithrombin (AT) and heparin cofactor II to various coagulation factors, which prevents their participation in the coagulation cascade (see Figure 58-3). I recommend the use of intravenous and/or subcutaneous heparin therapy as part of the acute management for thromboembolism because of the rapidity of onset of anticoagulation and the proven efficacy in human thrombotic disorders. In one study of cats treated with SK, cats additionally receiving heparin were more likely to survive, although the difference did not achieve statistical significance.[10] Heparin is absorbed rapidly from subcutaneous injection sites.[50] It should not be administered intramuscularly because of injection site hemorrhage.

No outcome-based studies have evaluated any particular dosage of heparin for cats with thromboembolism, and recommendations are highly variable. In one retrospective report of cats with ATE, initial IV dosages ranged from 75 to 500 U/kg.[2] Subcutaneous therapy was administered at dosages ranging from 10 to 300 U/kg q6-12h. The majority of cats received either 50 to 100 U/kg ("low-dose") or 200 to 250 U/kg ("high-dose") of heparin q6-8h.[2,10,22]

Clinical trials in human beings have suggested that plasma heparin concentrations of 0.35 to 0.70 U/ml (as measured by chromogenic factor Xa assay) are associated with the greatest clinical efficacy and least hemorrhagic complications.[51] In one investigation using normal cats, doses of 300 U/kg SQ q8h were associated most consistently with this target plasma concentration.[50] However, in cats with ATE, wide interindividual variation exists in heparin pharmacokinetics, with some cats requiring much higher doses (up to 475 U/kg) to maintain plasma levels in the therapeutic range recommended for human beings.[52]

Heparin use may be monitored using a chromogenic factor Xa assay, the APTT, or activated clot time (ACT). The suggested target is a 1.5-fold to 2.5-fold prolongation in APTT, when compared with normal plasma control, or prolongation of the ACT by 15 to 20 seconds. These prolongations were adapted from studies in human beings and have not been validated for cats. Wide variation in the sensitivity of APTT reagents and in individual patients' APTT responses to a given heparin concentration results in inconsistencies in degree of anticoagulation measured with this approach. The ACT is even less predictive of plasma heparin concentration.[50,52,53] Further, in one report of cats with ATE, a 1.5-fold to 2.0-fold prolongation in APTT occurred at plasma heparin concentrations well below the recommended therapeutic range for human beings in most cases.[52]

Low-Molecular-Weight Heparin

Small heparin polysaccharides are unable to bind thrombin and AT simultaneously. Consequently, low-molecular-weight (LMW) heparin is unable to catalyze the inactivation of thrombin by AT but retains the ability to enhance the inhibition of factor Xa by AT. For equivalent antithrombotic effect, LMW heparin is associated with less bleeding than UF heparin and also requires less frequent administration.[51] Unfortunately, limited information has been published regarding cats on any of the commercially available LMW heparins. A pilot study of dalteparin (Fragmin, Pharmacia, Kalamazoo, MI) in normal cats given at 100 U/kg or 200 U/kg q24h for 5 days indicated that the lower dose resulted in adequate plasma levels based on chromogenic FXa activity assay, but dose interval was not evaluated. In one cat in which plasma levels were checked repeatedly on day 5, heparin level fell below therapeutic range by 8 hours post dose.[54] A separate study of the pharmacokinetics of enoxaparin (Lovenox, Aventis, Bridgewater, NJ) in normal cats suggested an appropriate starting dose of 100 U/kg SQ q24h.[55] A recent study of enoxaparin and dalteparin pharmacokinetics in normal cats also indicated loss of anticoagulant effect by 8 hours after subcutaneous administration and described variability in response between individuals.[56] In three clinical feline patients in which I have attempted long-term therapy with enoxaparin starting at 100 U/kg SQ q24h, FXa activity assay monitoring indicated that the dose was appropriate, but the dose interval was inadequate. Two cats needed to receive the drug q12h and one needed it q8h to maintain levels in therapeutic range.[57] The appropriate dose regimen for LMW heparins may require administration more than q24h, and pharmacokinetics may be variable in sick cats, as was identified with unfractionated heparin.[52]

Because LMW heparins do not bind to thrombin, they have little impact on the APTT. The chromogenic FXa activity assay is required to assess plasma heparin levels. This assay is now available commercially through the Cornell University Coagulation Laboratory. Submission information may be obtained at http://web.vet.cornell.edu/public/coaglab/heparin.htm. It appears that, based on studies in human beings and experimental animals, and my personal experience with multiple cats, once the appropriate dose regimen has been determined via activity assay for the individual patient, plasma levels are fairly consistent over time.

Potential adverse effects of heparin therapy include hemorrhage,[58] heparin-induced thrombocytopenia[51] (not yet reported in a cat), and osteoporosis[51] (seen in one case I treated with long-term unfractionated heparin therapy for 18 months). In human beings, all of the adverse effects of heparin appear less frequent when LMW heparins are used.[51] Standard unfractionated heparin is relatively inexpensive. Markedly higher costs associated with use of the LMW heparins may limit their use in veterinary patients.

Platelet Antagonists

Acetylsalicylic acid (aspirin) is a cyclo-oxygenase inhibitor that inhibits the production of thromboxane A_2 (TXA_2) in platelets irreversibly. Because TXA_2 is a potent platelet aggregator and vasoconstrictor, aspirin decreases platelet aggregability and vasoconstriction in response to injury. No controlled trials have evaluated the efficacy of aspirin for acute management of ATE in cats, but in an experimental model, cats given 650 mg aspirin PO 1 hour before thrombus occlusion of the aorta had better collateral circulation than non–aspirin-treated controls.[59]

Abciximab, a glycoprotein (GP) IIb/IIIa receptor antagonist, was evaluated in a model of arterial injury in cats. Cats received either aspirin alone or aspirin plus abciximab. Cats in the second group that received both drugs had evidence of significant inhibition of platelet function and less thrombus formation.[60]

PROGNOSIS

Appendicular Arterial Thromboembolism

Feline ATE is associated with a poor prognosis. Reported rates of survival to discharge are 33 to 39 per cent.[2,9,10,22] Euthanasia is common at 24 to 35 per cent.[2,9,22] Most reports do not distinguish between euthanasia with no attempt to treat and euthanasia resulting from deterioration or lack of response to treatment. Clearly this is an important distinction, because it introduces the influence of clinician bias and owner commitment in the face of a disease with a poor prognosis. In one study, survival to discharge was 45 per cent when cases that were euthanized with no attempt to treat were excluded from the analysis.[2] Furthermore, survival in that study improved gradually over the 10 years reviewed, with 73 per cent of cats treated for acute limb ATE in the year 2001 surviving to discharge.

Significant differences between survivors and nonsurvivors have been reported for rectal temperature[2,10] and heart rate,[2] both higher among survivors. Having only one limb affected[2,9] and the presence of motor function[2] were significantly more frequent among survivors. Serum phosphorus concentration was slightly but significantly higher among nonsurvivors.[2] The presence of concurrent CHF did not affect survival to discharge from the hospital, but median survival after discharge for cats with CHF was markedly shorter than for cats without CHF.[2] Data from the cats with acute ATE that made up the University of Minnesota retrospective study were used to develop a logistic regression model to predict the probability of survival to discharge. Once rectal temperature was included in the model, no other variable improved the accuracy of prediction. This model predicts a 50 per cent probability of survival at a rectal temperature on admission of 37.2° C (98.9° F) (Figure 58-7). The model classified 67 per cent of survivors and 79 per cent of nonsurvivors correctly.[2]

Pulmonary Thromboembolism

All of the individual reported cases of feline patients with pulmonary thromboembolism were diagnosed via postmortem examination.[3,5,31,61] This would suggest that feline PTE is associated with a high mortality rate. However, the challenge of antemortem diagnosis is so significant that it is likely that many nonfatal cases of PTE are never suspected, much less diagnosed definitively. Consequently, estimation of the true prognosis associated with feline PTE is difficult.

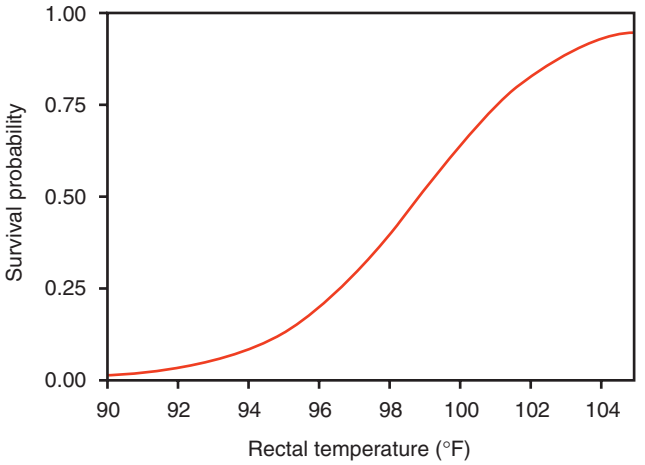

Figure 58-7. Logistic regression model predicting probability of survival to discharge for cats with arterial thromboembolism based on rectal temperature at admission. The model predicts a 50 per cent probability of survival at a temperature of 37.2° C (98.9° F).[2]

SUMMARY

Thromboembolism is a devastating complication of many common and uncommon feline diseases. Despite significant improvement in our understanding of the underlying causes and clinical features of thromboembolism in cats, many questions remain unanswered. Prediction of occurrence of thromboembolism is extremely difficult, clinical suspicion for pulmonary thromboembolism is still low, and definitive diagnosis is problematic. Management of thromboembolism remains a challenge, and mortality rates are high. The reader is directed to Chapter 37 for further discussion on this subject.

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Chapter 59

DIAGNOSIS OF ANEMIA

Rick L. Cowell, Ronald D. Tyler, and James H. Meinkoth

Anemia is a decrease in red blood cell (RBC) mass and is recognized typically by a decrease in the hematocrit, hemoglobin concentration, and red blood cell count. It is a frequently encountered clinical problem that can be caused by many diverse etiologies and may be life threatening if not treated properly. Causes of anemia can be divided into three general categories: RBC loss (hemorrhage), increased RBC destruction (hemolysis), and decreased RBC production (erythroid hypoplasia). These may occur alone or in any combination, depending on the disease process and complicating factors.

Each of the three general categories can be caused by many specific etiologies and can be subclassified to reflect common causative processes. *Hemorrhage* is caused by vessel injury (e.g., laceration, blunt trauma, and parasitic infestation) or by impaired coagulation (e.g., factor VIII deficiency, vitamin K deficiency/antagonism). *Hemolysis* may be intravascular (e.g., some toxins), extravascular (e.g., some erythroparasites), or both intravascular and extravascular (e.g., some cases of immune-mediated hemolytic anemia). *Erythroid hypoplasia* may be caused by myelophthisis/myeloproliferative disorders (e.g., lymphoma), endocrine dysfunction (e.g., decreased erythropoietin production resulting from chronic renal disease), or toxicity.

Obviously, successful treatment depends upon diagnosis of the specific causative etiology or etiologies. Rapid, accurate, and efficient diagnosis of anemia to allow quick institution of effective therapy is facilitated by a logical, methodical approach. The algorithmic approach depicted in Figure 59-1 and discussed in this chapter is offered as a general approach. Of course, this or any other general approach should be altered as necessary to fit unique cases and clinical conditions.

DIAGNOSIS OF ANEMIA: A PRACTICAL APPROACH

Generally, the most effective and efficient approach to the diagnosis of an anemic cat is to identify any obvious cause(s) of the anemia, such as profuse bleeding from injuries, evidence of intestinal bleeding, or history of ingestion of rodenticide containing a vitamin K antagonist. If an obvious cause is identified, use of the diagnostic procedure appropriate for the condition can provide rapid confirmation, and appropriate therapy can be instituted. If an obvious cause is not identified (anemia of unknown cause), a methodical approach such as that given in Figure 59-1 and discussed below can be used to assist in efficient, accurate identification of the cause and allow appropriate therapeutic intervention.

The most effective first step in diagnosing an anemia of unknown cause is to determine whether the anemia is due to erythroid hypoplasia. Anemias caused by erythroid hypoplasia do not show evidence of increased RBC production in the peripheral blood and are referred to as nonregenerative anemias. Anemias that are caused by hemorrhage or hemolysis, on the other hand, do show evidence of increased RBC production in the peripheral blood and are referred to as regenerative anemias. In cases of regenerative anemia, it takes 2 or 3 days for evidence of increased RBC production to become apparent in peripheral blood, and 5 to 7 days for it to reach a maximal response. Therefore an anemia should not be classified as nonregenerative until the anemia is known to be present for 5 or more days. The term "preregenerative anemia" refers to a regenerative anemia of insufficient duration to show evidence of increased RBC production in peripheral blood.

CLASSIFICATION AS REGENERATIVE VERSUS NONREGENERATIVE

Classification of anemia as regenerative or nonregenerative is based on determination of whether the bone marrow is responding appropriately (adequately) to the anemia. Generally, this is accomplished by examination of a Wright's-stained peripheral blood smear for polychromatophilic erythrocytes (polychromasia) and/or by performance of a reticulocyte count.

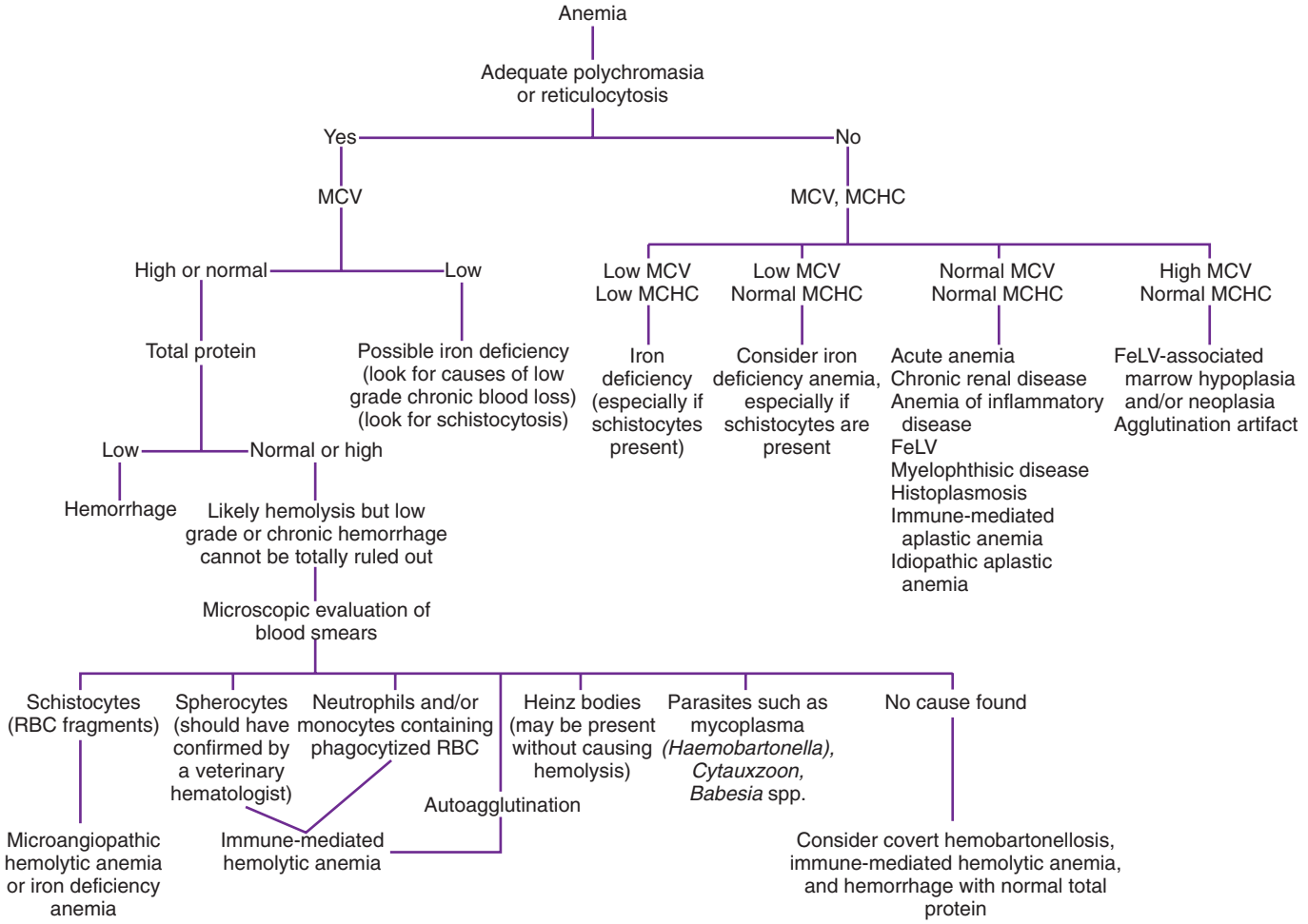

Figure 59-1. A flowchart to aid in the evaluation of the anemic cat. (Modified Fig. 41-1 from Diagnosis of Anemia [Chapter 41], Consultations in Feline Internal Medicine, vol 1, p. 336).

Table 59-1 | **Classification Scale for Evaluation of Anemia***

SEVERITY OF ANEMIA	HEMATOCRIT (%)	POLYCHROMATOPHILIC CELLS PER opf	RETICULOCYTES (%)	
			PUNCTATE	AGGREGATE
Mild	>20	1-3	>10	0.5-2
Moderate	15-20	3-4	>10	2-4
Marked	<15	>4	>10	>4

*Scale compares variations in hematocrit with the degree of polychromasia and the percentage of reticulocytes expected with a normal regenerative erythroid response.
Courtesy Oklahoma State University Clinical Pathology Teaching File.
opf, Oil power field.

Polychromatophilic Erythrocytes

Polychromatophilic erythrocytes (polychromasia) are young erythrocytes released from the bone marrow during the most recent 1 to 2 days. Polychromatophilic RBCs generally are larger than normal RBCs and stain a pale blue or grey (Figure 59-2). They are not fully hemoglobinized and contain polyribosomes staining blue and hemoglobin staining red, which results in their characteristic color. Increased numbers of polychromatophilic erythrocytes indicate that the bone marrow has responded to the anemia by increasing production and release of erythrocytes. Because the rate of increased erythrocyte production and release is proportional to the severity of anemia, the number of polychromatophilic erythrocytes in a peripheral blood smear generally is proportional to the severity of the cat's anemia if the ability of the bone marrow to respond to the anemia is not compromised. With stains that show polychromasia well (e.g., Wright's stains), the classification scale given in Table 59-1 may be used.

Polychromasia in Wright's-stained peripheral blood smears can be used to classify anemias as regenerative (adequately responsive) but should not be used to classify anemias as nonregenerative (inadequately responsive). This is because some cats tend to retain young (recently produced) erythrocytes in

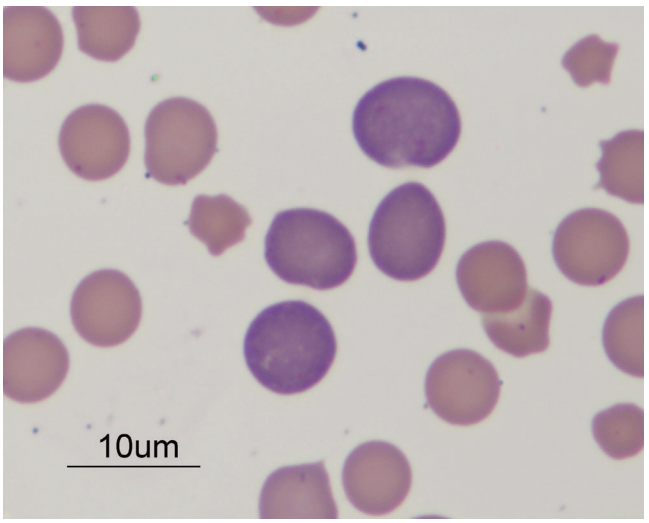

Figure 59-2. Four polychromatophilic erythrocytes are shown. Polychromatophilic erythrocytes are young erythrocytes and increased numbers indicate a regenerative anemia. (Courtesy Oklahoma State University, Clinical Pathology Teaching File.)

their bone marrow until the young erythrocytes are no longer polychromatophilic. This is especially true when the anemia is mild. Recognition is especially problematic with some hematological stains (e.g., Diff-Quik [Harleco] stains [Fisher Scientific, Middletown, VA]) that do not reveal polychromasia well. Therefore, if the peripheral blood smear shows sufficient polychromasia, the anemia can be classified reliably as regenerative. On the other hand, if polychromasia is insufficient to classify the anemia as regenerative, a reticulocyte count should be performed to determine whether the anemia is nonregenerative or regenerative but not showing prominent peripheral blood polychromasia.

Reticulocyte Counts

A reticulocyte count should be performed to evaluate anemic cats more accurately whose blood smears do not show sufficient polychromasia. Reticulocyte counts can be performed in-house or at a referral laboratory. To perform reticulocyte counts in-house, equal parts of fresh EDTA-anticoagulated blood and new methylene blue stain are placed in a test tube and mixed gently. The mixture is allowed to sit for 10 to 20 minutes at room temperature. After sitting, the tube is mixed well again to resuspend the erythrocytes. A smear of the mixture then is made using the same techniques as for making a blood smear. The smear is allowed to air-dry and then evaluated under the microscope at oil power (100× objective). The numbers of aggregate reticulocytes and punctate reticulocytes observed are recorded separately while counting 1000 total erythrocytes. The number of aggregate reticulocytes and the number of punctate reticulocytes then are converted to a percentage by moving the decimal point one space to the left to get the number of reticulocytes per 100 cells (e.g., if 40 aggregate reticulocytes are counted while counting 1000 total erythrocytes, the aggregate reticulocyte percentage is 4.0 per cent). Aggregate reticulocytes contain medium-to-large, dark-staining clumps of aggregated polyribosomes. In contrast, punctate reticulocytes contain small (punctate), dark-staining clumps of polyribosomes (Figures 59-3 and 59-4).

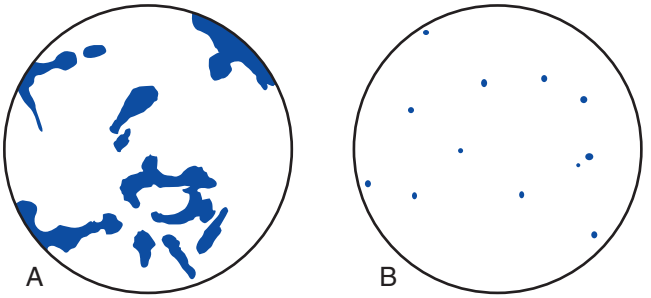

Figure 59-3. Schematic representation of feline reticulocytes. **A,** Aggregate reticulocyte containing medium-to-large dark-staining clumps of aggregated polyribosomes. **B,** Punctate reticulocyte containing small dark-staining clumps of polyribosomes. (Courtesy Oklahoma State University, Clinical Pathology Teaching File.)

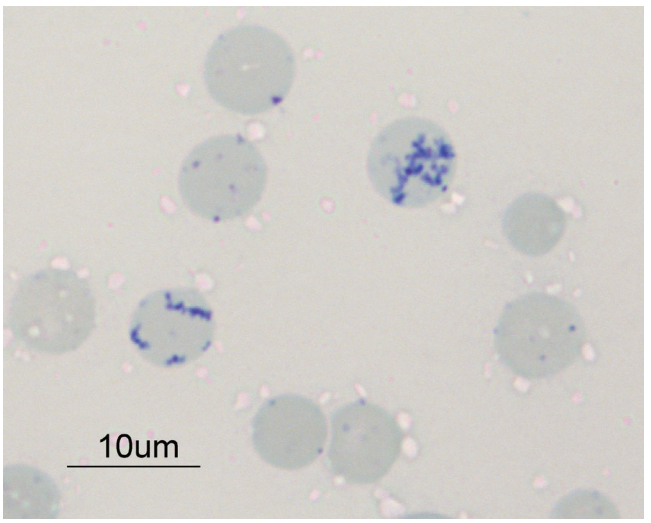

Figure 59-4. New methylene blue–stained blood smear showing aggregate and punctate reticulocytes. (Courtesy Oklahoma State University, Clinical Pathology Teaching File.)

When a commercial referral laboratory is used to obtain a reticulocyte count, an EDTA-anticoagulated blood sample should be submitted to the laboratory. Many commercial veterinary laboratories count and report only the aggregate reticulocyte percentage. This is not a major problem as long as the veterinarian is aware it is only an aggregate reticulocyte count, because reporting only aggregate reticulocytes can cause some mild, regenerative anemias to be misclassified as nonregenerative. When an unfamiliar laboratory is used (especially if it is not a veterinary laboratory), the submitting veterinarian must ensure the facility is familiar with feline reticulocytes and that they differentiate aggregate and punctate reticulocytes and report them separately. Some laboratories may report the total of both types as a single (total) reticulocyte count erroneously. Reporting the total of both types of reticulocytes as a single total reticulocyte count can result in nonregenerative anemias being misclassified as regenerative.

Interpretation of Reticulocyte Counts

Classification of anemia as adequately regenerative or inadequately regenerative using reticulocyte counts (see Table 59-1) is more complex in cats than in dogs, because two types (aggre-

gate and punctate) of reticulocytes are present. Also, the aggregate reticulocyte increase in cats is not as marked as the reticulocyte increase in dogs. Therefore anemias are termed regenerative at lower aggregate reticulocyte numbers in cats than the reticulocyte numbers used typically in dogs.

In cats, the percentage of aggregate reticulocytes is used to determine regenerative response with a moderate or marked anemia, whereas the percentage of punctate reticulocytes is used to determine regenerative response in mild anemias. The percentage of punctate reticulocytes is of importance in mild anemias, because the feline bone marrow tends to hold the developing reticulocytes through the aggregate stage during mild anemia and therefore release primarily increased numbers of punctate reticulocytes. In contrast, increased numbers of aggregate and punctate reticulocytes are released in moderate or marked anemias. Maturation of punctate reticulocytes to mature RBC is long, up to 14 days. As a result, punctate reticulocytes may accumulate to levels above the reference range in moderate or marked nonregenerative anemias, whereas aggregate reticulocyte numbers are not increased. Therefore only the aggregate reticulocyte count should be used to classify moderate and marked anemias as regenerative or nonregenerative.

On the other hand, punctate reticulocyte counts may be helpful in evaluation of mildly anemic cats. Mildly anemic cats with adequate bone marrow response may not have sufficiently increased aggregate reticulocyte counts to be classified as regenerative but have significantly increased punctate reticulocyte counts if the anemia is of sufficient duration (more than 7 days). Failure of the punctate reticulocyte count to be increased after 6 days of anemia suggests compromise of the ability of the bone marrow to respond.

If the bone marrow response to anemia, as determined by the amount of polychromasia or the reticulocyte count (see Table 59-1) is adequate, the anemia is classified as regenerative and is caused by hemorrhage or hemolysis. If the bone marrow has had sufficient time to respond but the response is inadequate (determined by an inappropriately low reticulocyte count), the anemia is classified as nonregenerative and is caused by erythroid hypoplasia/dysplasia. Further diagnosis of regenerative and nonregenerative anemias is depicted in Figure 59-1 and discussed below.

DIAGNOSIS OF REGENERATIVE ANEMIAS

Further diagnosis of regenerative anemias can be pursued by determining which of the two general processes that can cause regenerative anemia (hemorrhage and hemolysis) is present. Often hemorrhage can be differentiated from hemolysis quickly and easily by measurement of the patient's total serum or plasma protein (TP) concentration.

Total Protein

Total protein (TP) concentration can be estimated refractometrically in-clinic from serum or plasma, or serum may be submitted to a referral laboratory for chemical determination of the total protein level (included in most chemistry profiles). The normal range for plasma protein concentration is slightly higher than for serum protein concentration, because the total plasma protein level includes coagulation proteins (primarily fibrinogen) that are absent from serum.

Normal or High Total Protein Concentration

Normal or high TP concentrations in patients with regenerative anemia usually indicate hemolysis. These patients may or may not be icteric. If the hemolysis has an intravascular component, hemoglobinuria may be detected but often it is not present. Because differentiation of intravascular and extravascular hemolysis is unreliable and does little to advance the diagnostic process in cats, it is not used as a diagnostic step in the approach depicted in Figure 59-1 and is not discussed in this chapter. However, chronic mild hemorrhage, or more severe hemorrhage that has ceased several days before collection of the blood sample, often results in a regenerative anemia with normal or high TP concentration. These two situations should be considered and investigated if icterus is not detected and a cause of hemolysis is not identified (see discussion below).

Low Total Protein Concentration

Low TP concentration in patients with regenerative anemia supports a diagnosis of hemorrhage. If the source of hemorrhage is apparent (e.g., fleas, ticks, overt hemorrhage), further evaluation usually is unnecessary. When the source of hemorrhage is not apparent, gastrointestinal hemorrhage is likely and should be investigated.

DIAGNOSIS OF IRON DEFICIENCY ANEMIAS: INTERPRETATION OF MEAN CORPUSCULAR VOLUME AND MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION

Chronic hemorrhage results occasionally in early iron deficiency, which exacerbates the anemia but allows the anemia to continue to appear as regenerative (e.g., adequate polychromasia); however, the hematocrit fails to increase. If iron loss is severe, of long duration, and without iron supplementation, iron depletion may develop. Iron depletion exacerbates the anemia and causes it to appear nonregenerative (e.g., inadequate polychromasia and/or reticulocytosis). Evaluation of the mean corpuscular volume (MCV) is helpful in recognition of iron deficiency and depletion, especially with electronic cell counters. Unfortunately, evaluation of the mean corpuscular hemoglobin concentration (MCHC) is of less value in cats because it is seldom abnormal (hypochromic) in cats with iron deficiency anemia.

The MCV is the average RBC volume and therefore can be calculated by the following formula:

$$\text{MCV} = \text{Hematocrit} \times 10/\text{RBC count (in millions)}$$

However, most commercial laboratories currently use electronic cell counters that measure the cell volume instead of calculating it as described above. Also, these machines provide a histogram or computer graphic that allows the clinician to see subpopulations of microcytic erythrocytes before the MCV has decreased (e.g., because MCV is an average, it takes a major change before the average size of all erythrocytes is decreased [microcytic]).

The MCHC is the ratio of the weight of hemoglobin to the volume of erythrocytes. It is calculated by the following formula:

$$\text{MCHC} = \text{Hemoglobin} \times 100/\text{Hematocrit}$$

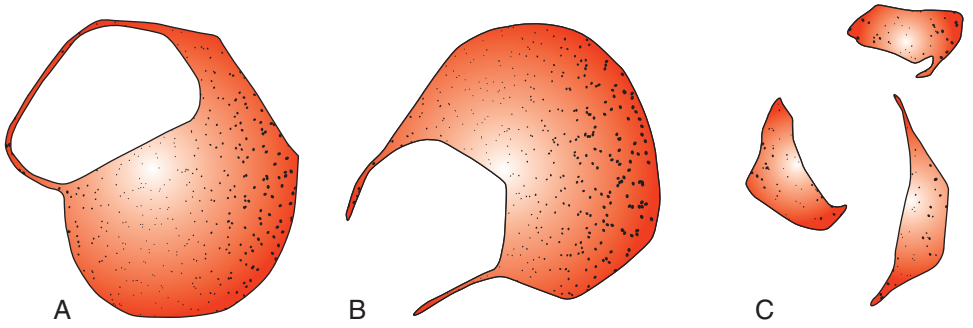

Figure 59-5. Schematic representation of erythrocyte fragments. **A,** Blister cell. **B,** Helmet cell. **C,** Schistocytes. (Courtesy Oklahoma State University, Clinical Pathology Teaching File.)

MCHC is helpful in most species for the detection of iron deficiency anemia. Unfortunately, most cats with iron deficiency anemia do not develop a low MCHC and hypochromia cannot be perceived on blood smear analysis, which makes MCHC and microscopic evaluation for hypochromia of less value in cats. Abnormal RBC shapes and schistocytes often are observed on blood smear examination.

Low MCV (Microcytic)

Microcytic anemia suggests iron deficiency or depletion and can appear as regenerative anemia or as nonregenerative anemia. During early iron deficiency, sufficient polychromasia and reticulocytosis often are present for the anemia to be classified as regenerative. As iron stores become exhausted, polychromasia and reticulocytosis decrease and the anemia appears nonregenerative. Most, if not all, iron-deficiency anemias in adult cats are caused by low-grade, chronic blood loss. As a result, the total protein (TP) concentration often is decreased concurrently. In kittens, the low content of iron in milk causes a normal transient iron deficiency and makes them more prone to develop pathologic iron-deficiency anemia with hemorrhagic diseases (e.g., parasites).

Normal or Increased MCV and Normal or Decreased MCHC

Classically, regenerative anemias are stated to be macrocytic and hypochromic. However, because MCV and MCHC are averages of the RBC population, they often are within reference limits during regenerative anemia in cats. Therefore, normocytic normochromic anemias should be considered regenerative if polychromasia and/or reticulocyte counts are increased sufficiently.

DIAGNOSIS OF HEMOLYTIC ANEMIAS: MICROSCOPIC EXAMINATION

Microscopic examination of Wright's-stained peripheral blood smears can be helpful in determining the cause of hemolysis. Optimal examination requires high-quality smears and careful avoidance of stain precipitate. If a referral laboratory is used for blood smear examination, the following should be submitted: two high-quality, air-dried blood smears; a tube of EDTA-anticoagulated blood; and a differential diagnosis based on clinical signs and history.

Erythrocyte Fragments

Erythrocyte fragments (Figures 59-5 and 59-6) such as schistocytes, blister cells, and helmet cells indicate a microangiopathic hemolytic process but also are a common finding in other conditions in cats such as iron-deficiency anemia. When schistocytes are the dominant finding in the peripheral blood smear, conditions causing microangiopathy (e.g., hemangiosarcoma, disseminated intravascular coagulation, iron deficiency) should be considered.

Spherocytes

Spherocytes are RBCs that are smaller (less than two thirds the size of a normal RBC) and stain more intensely than normal erythrocytes. Because normal cat erythrocytes have minimal or no central pallor, detection of feline spherocytes is difficult and is an uncommon and inconsistent finding even for those clinical pathologists with considerable experience. Although a few spherocytes may be found with conditions other than immune-mediated hemolytic anemia (e.g., iron-deficiency anemia, microangiopathic anemia, RBC parasites), detection of spherocytes without the presence of schistocytes supports a diagnosis

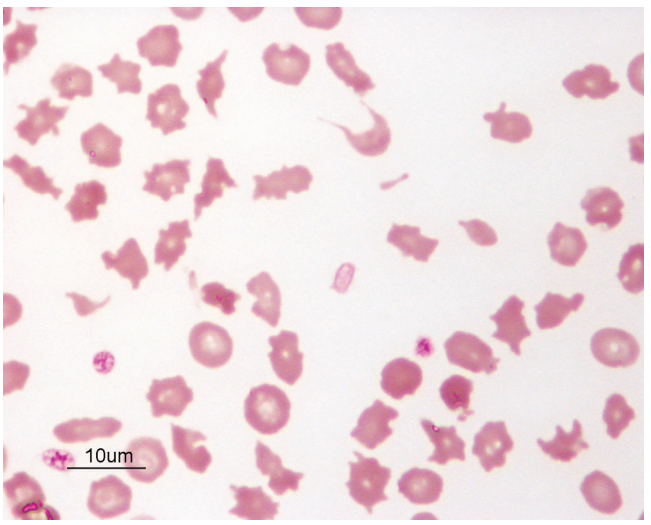

Figure 59-6. Erythrocyte fragments (schistocytes and keratocytes [bite or helmet cells]) in a blood smear from a cat. (Courtesy Oklahoma State University, Clinical Pathology Teaching File.)

of immune-mediated hemolytic anemia. Again, spherocytes in feline blood are difficult to find and generally are absent. The Coombs' test may be useful in confirming an immune-mediated hemolytic anemia.

Erythrophagocytosis

Circulating monocytes phagocytize antibody-coated erythrocytes occasionally. Also, identification of erythrophagocytosis by monocytes on peripheral blood smears strongly suggests an immune component to the anemia. Erythroparasites such as *Mycoplasma haemofelis* (formerly *Haemobartonella felis*) elicit an immune response, and on rare occasion, macrophages containing phagocytized RBCs may be seen on peripheral blood smears (see Chapter 63). Rarely, neoplastic lymphoid cells may phagocytize erythrocytes. This finding suggests lymphoid neoplasia instead of immune-mediated hemolytic anemia.

Autoagglutination

Occasionally, autoagglutination may be observed as RBC clumping in the EDTA tube or on blood smears. However, RBC clumping can be caused by rouleaux formation and autoagglutination. Autoagglutination is random, disorganized clumping of RBCs, and its presence is diagnostic of immune-mediated hemolytic anemia. In contrast, rouleaux formation is organized stacking (like coins) of RBCs (Figure 59-7).

Rouleaux formation may be more prominent in strongly inflammatory conditions. As inflammatory protein concentrations increase, some of these proteins adhere to the surface of phospholipid membranes or "coat the surface of erythrocytes." These proteins are positively charged and therefore cause a decrease in the net negative charge (zeta-potential) of the erythrocyte. This allows increased contact between RBCs, which enhances rouleaux formation.

When autoagglutination is suspected, it should be differentiated from rouleaux formation by a saline dilution test. This test is performed by placing a drop of EDTA-anticoagulated blood on a glass slide. Three or four drops of physiological saline then are placed on the drop of blood. A coverslip is placed over the mixture, which is observed unstained under a microscope using the 40× objective. The substage condenser should be lowered to allow for more light scattering, because this mixture is being evaluated unstained and phospholipids in membranes have a low refractive index. If the clumping is caused by rouleaux, either the RBC clumps have dispersed or the rouleaux pattern is recognized easily. If the clumping is caused by autoagglutination, disorganized RBC clumps are present and can be recognized easily as autoagglutination.

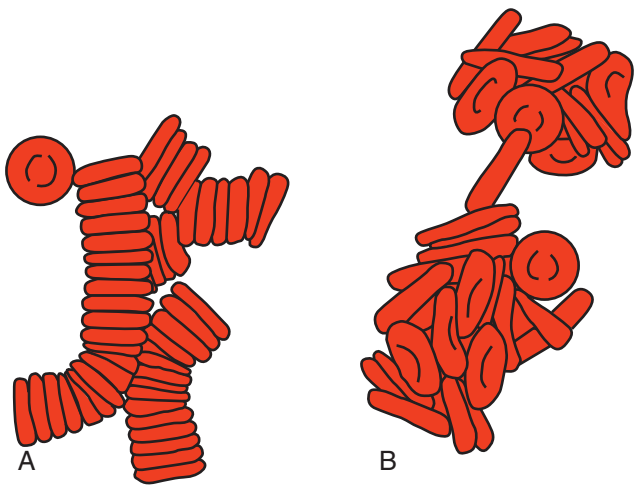

Figure 59-7. Schematic representation of red blood cell clumping. **A,** Rouleaux formation is an organized stacking (like coins) of erythrocytes. **B,** Autoagglutination is a random, disorganized clumping of erythrocytes. (Courtesy Oklahoma State University, Clinical Pathology Teaching File.)

Heinz Bodies

Heinz bodies are clumps of denatured hemoglobin and often are seen projecting from the surface of the RBCs. Heinz bodies stain the same color as the RBC cytoplasm with Wright's stain, slightly clear with Diff-Quik stain, and dark blue or black with new methylene blue stain (Figure 59-8). Small Heinz bodies may be present in up to 5 per cent of the erythrocytes in healthy cats and in higher numbers in some disease states. Because cats

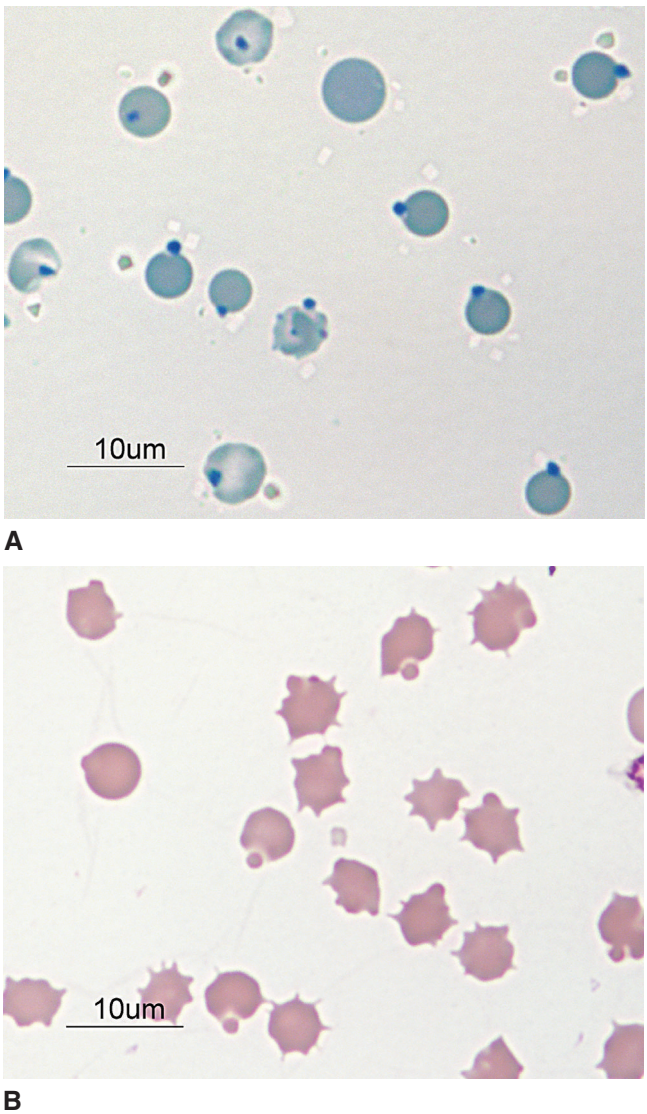

Figure 59-8. A, New methylene blue–stained blood from a cat showing Heinz bodies projecting from RBC. **B,** Wright's-stained blood smear showing a Heinz body projecting from a RBC. (Courtesy Oklahoma State University, Clinical Pathology Teaching File.)

have a nonsinusoidal spleen, they tolerate small Heinz bodies. However, when large Heinz bodies are found in peripheral blood smears of cats with hemolytic anemia, Heinz body hemolytic anemia (oxidant-induced anemia) should be suspected, especially if hemoglobinuria is observed. Some causes of Heinz body hemolytic anemia include onion ingestion and acetaminophen toxicity.

Parasites

M. haemofelis (formerly *H. felis*) (Figure 59-9) and *Cytauxzoon felis* (Figure 59-10) can cause hemolytic anemia in cats. Depending on one's practice area, either cytauxzoonosis or hemobartonellosis may be the most common. Cats with cytauxzoonosis invariably are extremely ill, may show neurological signs, and often resemble cats with *M. haemofelis* (hemobartonellosis) clinically. It should be remembered that, although identification of any of these hemoparasites establishes a diagnosis, failure to find them does not exclude them. In areas where *M. haemofelis* (*H. felis*) is enzootic, it is prudent to treat cats with undiagnosed regenerative hemolytic anemia with tetracycline to prevent cases of covert hemobartonellosis from being untreated (see Chapter 63).

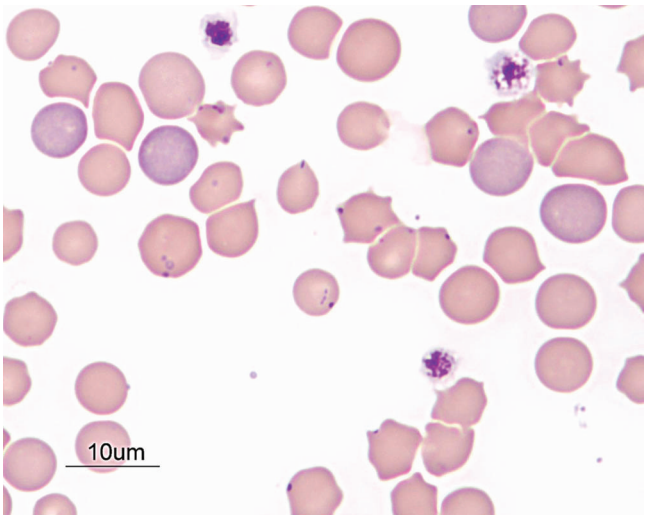

Figure 59-9. Rod and ring forms of *Mycoplasma* (*Haemobartonella*) organisms present on RBCs. Polychromatophilic RBCs are pictured also. (Courtesy Oklahoma State University, Clinical Pathology Teaching File.)

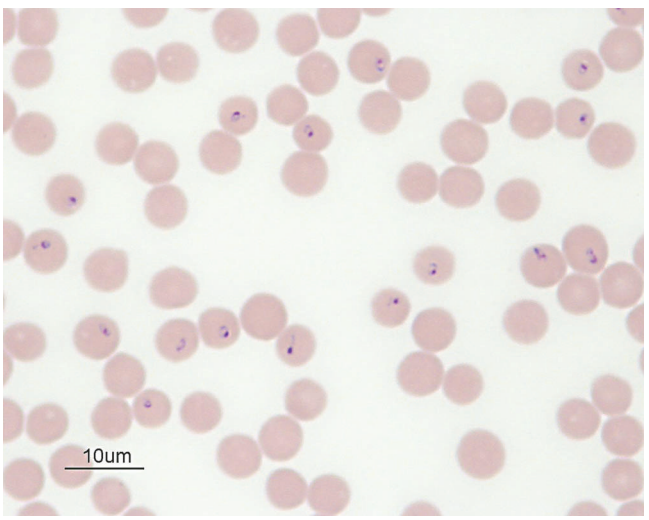

Figure 59-10. Ring form of *Cytauxzoon felis* is present within numerous RBCs. (Courtesy Oklahoma State University, Clinical Pathology Teaching File.)

No Cause Found

When the cause of the hemolytic process cannot be identified or implied by peripheral blood smear examination, conditions such as covert *M. haemofelis* infection (hemobartonellosis), immune-mediated hemolytic anemia, bone marrow recovering from a marrow insult, chronic mild hemorrhage, and hemorrhage that ceased several days before blood collection should be considered.

DIAGNOSIS OF NONREGENERATIVE ANEMIAS

If the degree of polychromasia/reticulocytosis is inadequate for the degree of anemia (see Table 59-1), the anemia is classified as nonregenerative. An effective first step in the diagnosis of nonregenerative anemia is to evaluate the MCV and MCHC.

Low MCV and Normal MCHC

Microcytic, normochromic anemias suggest iron deficiency/depletion, especially if schistocytosis is present. Iron-deficiency anemia in cats typically is not microcytic (low MCV), hypochromic (low MCHC) as it is in other species. Because iron-deficiency anemias in adult cats are usually, if not always, caused by low-grade, chronic blood loss, TP concentration should be evaluated to see if it is decreased to help confirm the presence of blood loss. However, in cases of iron deficiency resulting from chronic mild hemorrhage, TP concentrations may be within reference limits. Therefore a normal TP concentration does not exclude a diagnosis of blood loss and iron-deficiency anemia.

During early iron deficiency, sufficient polychromasia and reticulocytosis often are present for the anemia to be classified as regenerative. As iron stores become exhausted (iron depletion), polychromasia and reticulocytosis decrease and the anemia may appear nonregenerative. Adequate parenteral iron supplementation usually causes the anemia to become regenerative within several days. Of course, the source of blood loss should be sought and treated. When the cause of blood loss (e.g., fleas, ticks, overt hemorrhage) is not apparent, gastrointestinal hemorrhage should be considered and investigated.

Normal MCV and MCHC

Normocytic, normochromic anemias (anemias with normal MCV and MCHC) that have inadequate polychromasia/reticulocytosis can be caused by diseases such as feline leukemia virus (FeLV)–induced bone marrow hypoplasia, myelophthisic disease (e.g., myeloproliferative disease, lymphoma), anemia of inflammatory disease (anemia of chronic disease), chronic renal disease, histoplasmosis, immune-mediated aplastic anemia, pure red cell aplasia, idiopathic aplastic anemia, and acute (duration of less than 3 days) regenerative anemia (sometimes called "preregenerative" anemia).

A diagnosis of acute regenerative anemia usually can be established or ruled out by a complete history, thorough physical examination, and determination of the TP. Acute hemorrhage sufficient to cause significant anemia also should lower the total protein concentration. Often the source of hemorrhage can be identified during physical examination or hemorrhagic episode(s) recounted in the history.

Acute hemolysis sufficient to cause significant anemia usually produces icterus. However, icteric patients that do not show evidence of bone marrow regeneration after 4 or 5 days of anemia may have a nonregenerative anemia with concurrent liver disease (such as neoplastic infiltration of the liver).

Investigation of normocytic, normochromic nonregenerative anemia usually is aided by a complete hemogram (including platelet count), serum chemistry profile, feline immunodeficiency virus and FeLV testing, and in some cases cytological bone marrow examination.

Leukemia resulting from myeloproliferative disease or lymphoid leukemia sometimes is recognizable in peripheral blood smears (Figures 59-11 and 59-12). On other occasions, the hemogram may reveal neutropenia, thrombocytopenia, or pancytopenia, suggesting bone marrow suppression. Cytological examination of the bone marrow often is rewarding in cases of myeloproliferative disease.

The degree of anemia caused by chronic renal disease is somewhat proportional to the degree of decreased glomerular filtration rate, and the blood (serum) urea nitrogen and creatinine concentrations are markedly increased by the time significant anemia has developed. Therefore markedly increased blood urea nitrogen and serum creatinine concentrations with isosthenuric urine specific gravity strongly support chronic renal disease as the cause of the anemia. On the other hand, normal or only mildly elevated serum urea nitrogen and creatinine concentrations make chronic renal disease less likely as the cause of the anemia.

If icterus is present, the direct bilirubin level is greater than the indirect bilirubin, and hepatic enzymes are moderately or markedly increased, conditions that can cause concurrent bone marrow suppression and liver disease should be considered. Some important considerations include lymphoma, myeloproliferative disease, cytauxzoonosis, and histoplasmosis. These conditions usually are associated with bone marrow infiltration when the liver is affected and, as a result, bone marrow examination usually is diagnostic. Cytological bone marrow examination is effective in diagnosing nonregenerative anemia caused by histoplasmosis. With cytauxzoonosis, organisms may not be present in the peripheral blood early in the disease process. Repeat hemograms usually yield a diagnosis. However, bone marrow cytology may allow for a definitive diagnosis more quickly by finding macrophages containing developing merozoites of *C. felis*.

Feline leukemia virus often causes nonregenerative anemia by bone marrow suppression. Some cases of FeLV-induced bone marrow suppression are associated with lymphoma or myeloproliferative disease, but others are not. These anemias (whether or not they are associated with neoplasia) may be normocytic normochromic or macrocytic normochromic. FeLV-induced bone marrow suppression should be suspected in FeLV-positive cats with otherwise unexplained nonregenerative anemia. Bone marrow examination usually is helpful in investigating these cases. Indirect fluorescent antibody testing of bone marrow smears for FeLV may be of value in cases of normocytic, normochromic nonregenerative anemias or macrocytic, normochromic nonregenerative anemias that are not diagnosed by a complete hemogram, serum chemistry assay, peripheral blood FeLV testing, and cytological bone marrow examination.

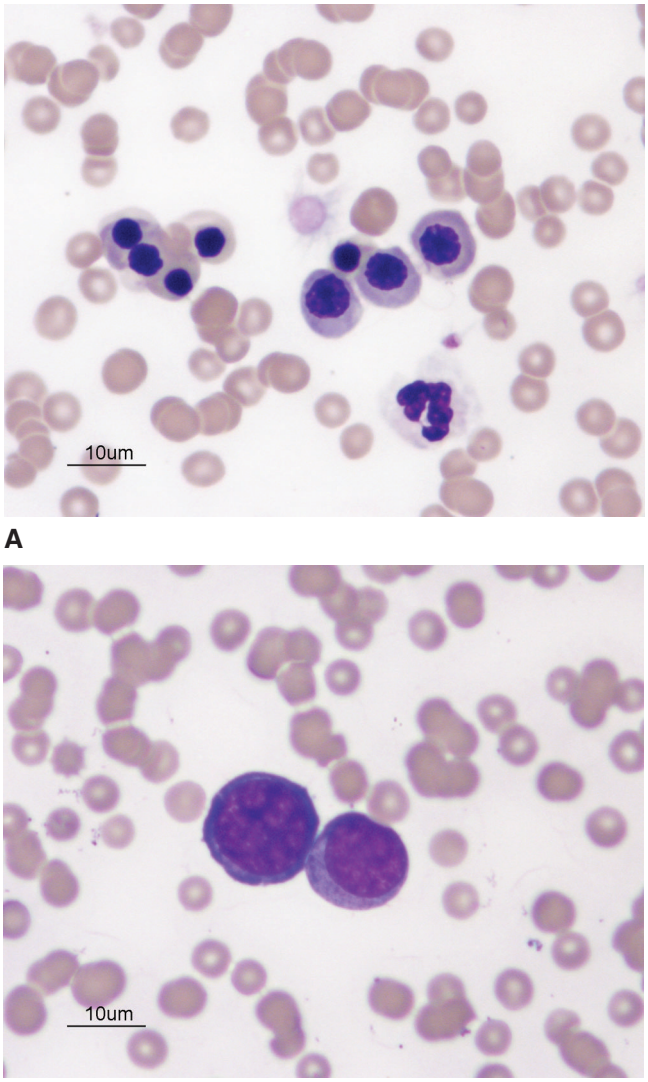

Figure 59-11. A, Many nucleated RBCs and no polychromasia. **B,** Rubriblasts in a blood smear from a cat with erythroleukemia (M6Er). (Courtesy Oklahoma State University, Clinical Pathology Teaching File.)

The absence of a positive test for FeLV does not exclude FeLV-induced disease completely. However, if FeLV infection is not detected, anemia of inflammatory disease, pure red cell aplasia, immune-mediated aplastic anemia, and idiopathic aplastic anemia should be considered. Anemia of inflammatory disease causes only mild to moderate anemia (hematocrit generally above 20 per cent) and usually is associated with an inflammatory leukogram. Typically, bone marrow examination reveals myeloid hyperplasia and erythroid hypoplasia with marrow plasmacytosis and hemosiderosis. When anemia of inflammatory disease is suspected, the site of inflammation should be sought and treated.

If evidence of anemia of inflammatory disease is not found and/or the anemia is marked, immune-mediated aplastic anemia

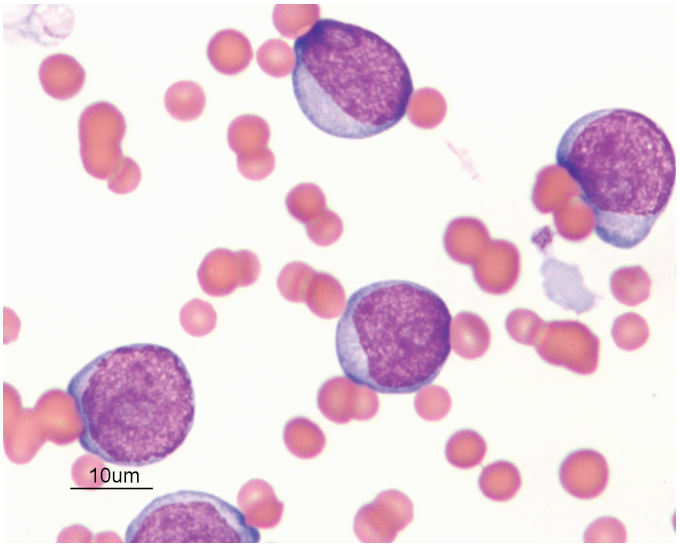

Figure 59-12. Large blast cells indicating leukemia are present on a peripheral blood film. The blast cells are lymphoblasts secondary to lymphoblastic leukemia. (Courtesy Oklahoma State University, Clinical Pathology Teaching File.)

and idiopathic aplastic anemia should be considered. No diagnostic test is available for identification of these two conditions. Remission of anemia subsequent to immunosuppressive therapy supports a diagnosis of immune-mediated aplastic anemia.

High MCV and Normal MCHC

Macrocytic, normochromic nonregenerative anemias (anemias with high MCV and normal MCHC values) usually are caused by FeLV-induced bone marrow suppression (with or without development of lymphoid leukemia or myeloproliferative disease); however, on rare occasions, they may be associated with an agglutination artifact. Laboratory error or artifactual increase in the MCV resulting from agglutination can be recognized easily on blood smear examination.

Most cats with FeLV-induced macrocytic, normochromic nonregenerative anemia test positive for FeLV by both indirect fluorescent antibody and enzyme-linked immunosorbent assay (ELISA) techniques; some affected cats test negative by indirect fluorescent antibody tests and positive by ELISA tests; and a few cats test negative by both procedures. Occasionally, FeLV can be identified only by indirect fluorescent antibody testing of bone marrow smears.

Some cats with lymphoid leukemia or myeloproliferative disorders (e.g., erythroleukemia [M6Er]) will be sufficiently leukemic to be diagnosed by peripheral blood smear examination, but others will not. Total white blood cell counts may be low, normal, or elevated in cats with lymphoid leukemia or myeloproliferative disease. Cytological bone marrow examination usually is effective in demonstrating lymphoid leukemia and myeloproliferative disease when they are present.

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Chapter 60

PLATELET DISORDERS

Andrew Mackin

Platelet disorders are reported uncommonly in cats. Furthermore, when such disorders occur, they often are subclinical or well tolerated. However, a number of potentially important platelet disorders are observed occasionally in cats, including thrombocytopenia (decreased platelet number), thrombocytosis (increased platelet number), and thrombocytopathy (decreased platelet function). Thrombocytopenia, the most common platelet disorder, has been reported to occur in only about 1 to 3 per cent of feline blood samples submitted for hematology.[1,2] However, although genuine and significant thrombocytopenia is relatively uncommon in cats, veterinary practitioners commonly encounter a fictitiously low platelet count, which is a major cause of diagnostic confusion.[2,3] Because the erroneous diagnosis of thrombocytopenia potentially can lead to unnecessary further diagnostic tests and therapy, even an incorrectly diagnosed "low platelet count" can have a significant impact on the health of the feline patient.

NORMAL HEMOSTASIS

Hemostasis is a complex process involving vasculature, platelets, and coagulation proteins. Hemostasis is divided into a vascular/platelet phase (primary hemostasis) and a subsequent coagulation phase (secondary hemostasis). Platelets play a central role in primary hemostasis (Figure 60-1).

Primary hemostasis starts with vasoconstriction triggered by vessel injury and continues until vessel integrity is restored and bleeding stops. Platelets respond to vessel injury by adhering to exposed vascular subendothelium (platelet adhesion) and other platelets (primary aggregation), changing shape, and releasing substances that promote vasoconstriction and activate even more platelets (the release reaction). Platelet adhesion is facilitated by von Willebrand factor (vWF), a large glycoprotein that circulates in platelets and plasma and links platelet surface membranes to subendothelial proteins such as collagen. Platelet contraction and aggregation triggered by substances released by the platelets (secondary aggregation) continue until the injury is sealed by a fragile platelet plug. Although fragile, this platelet plug is sufficient to prevent significant bleeding from the numerous minor vascular endothelial injuries associated with normal day-to-day living. Primary hemostasis alone, however, is beneficial only temporarily unless the platelet plug is reinforced by fibrin strands assembled by the clotting cascade (secondary hemostasis), particularly with more major vessel injuries.

Platelets are small, nonnucleated cells composed of membrane-bound cytoplasm formed via the fragmentation of megakaryocytes, large multinucleated cells located within the bone marrow. Marrow platelet production commences with a pluripotent hemopoietic stem cell, which gives rise to a megakaryocytic progenitor cell. These progenitor cells differentiate into megakaryoblasts, which in turn mature into megakaryocytes. Subsequent fragmentation of a single megakaryocyte may release many thousands of platelets into the circulation. The entire process of marrow platelet production (thrombopoiesis) lasts 3 to 4 days.[4] Circulating platelets in cats have a survival time of only about 1 to 2 days.[5] Aged (senescent) platelets then are removed from the circulation by the mononuclear phagocytic system, particularly within the spleen and liver.

CLINICAL SIGNS

Significant decreases in either platelet number or function in cats usually present as typical disorders of hemostasis, manifested as excessive bleeding tendencies.[1,6,7] Paradoxically, significant increases in platelet number also can manifest as a typical bleeding disorder if thrombocytosis is associated with platelet dysfunction.

Careful questioning of the owners of a cat with a chronic platelet disorder may reveal a long history of hemorrhage from multiple unrelated sites, although cats with more acute defects may present initially with bleeding from only one site.[6,7] The veterinarian should be aware that some manifestations of hemostatic disorders may not be recognized by owners as bleeding, particularly petechial and ecchymotic hemorrhages, melena, and hematemesis. Cats with severe hereditary disorders of platelet function typically develop episodic spontaneous hemorrhage at an early age.[7] Cats with milder defects, however, may not be recognized until significant vessel injury occurs (trauma or elective procedures such as neutering, dentistry, or nail clipping)[7,8] or a second disease process develops that further compromises hemostasis. Severe hereditary defects are unlikely to be present in a cat that previously has experienced major surgery or trauma without associated excessive bleeding.

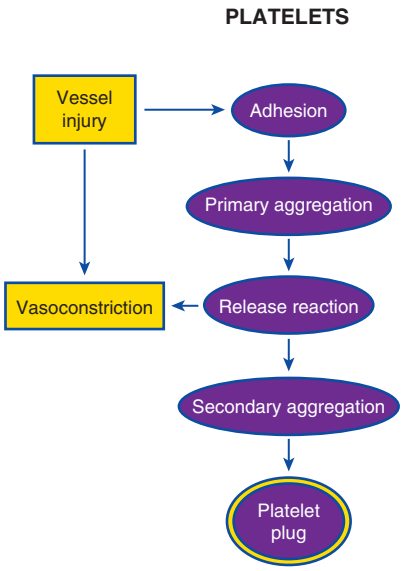

Figure 60-1. The central role of platelets in primary hemostasis.

Cats with severe platelet disorders present typically with multifocal pinpoint (petechial) hemorrhages affecting the skin and mucous membranes, because platelets fail to seal even the tiny traumatic capillary defects associated with normal activity,[1,6-8] although petechiae appear to occur less commonly in cats than in dogs.[1] Petechiae may merge into small, flat bruises (ecchymoses) and occur most commonly at pressure points, on ventral skin surfaces, and at other sites of vessel trauma (Figure 60-2). Ocular hemorrhage (conjunctival, scleral, iridal, and retinal petechiae, and hyphema) sometimes is reported.[1,8] Signs of external hemorrhage, such as epistaxis, hematemesis, melena, and hematuria, also can be observed.[1,7] Cats suffering from severe or prolonged external blood loss, particularly into the gastrointestinal tract, may become hypovolemic and/or anemic.[8] Intact secondary hemostasis often prevents major hemorrhage into joints or body cavities.

Cats with profound platelet disorders often appear to be stable or even clinically normal.[9,10] Compared with other species, cats appear able to tolerate major hemostatic defects for surprisingly long periods without obvious bleeding, perhaps in part because their sedentary lifestyle sometimes averts vessel trauma. Cats with major platelet disorders, however, should be considered highly susceptible to serious and potentially fatal hemorrhage and should be regarded therefore as "ticking time-bombs."

THROMBOCYTOPENIA

The normal reference range for platelet counts in cats is reported to be approximately 300 to 800 $\times$ 10^9 platelets/L (300,000 to 800,000 platelets/µL),[4] although reference ranges vary with different clinical pathology laboratories and different counting methods. Thrombocytopenia, strictly defined, is any platelet count less than 300 $\times$ 10^9 platelets/L, although rarely do platelet counts above about 100 to 150 $\times$ 10^9 platelets/L have any real diagnostic or clinical significance. In fact, cats produce far more platelets than are needed to maintain hemostasis, and platelet numbers typically must fall to less than 10 per cent of normal values before spontaneous bleeding is observed.[1]

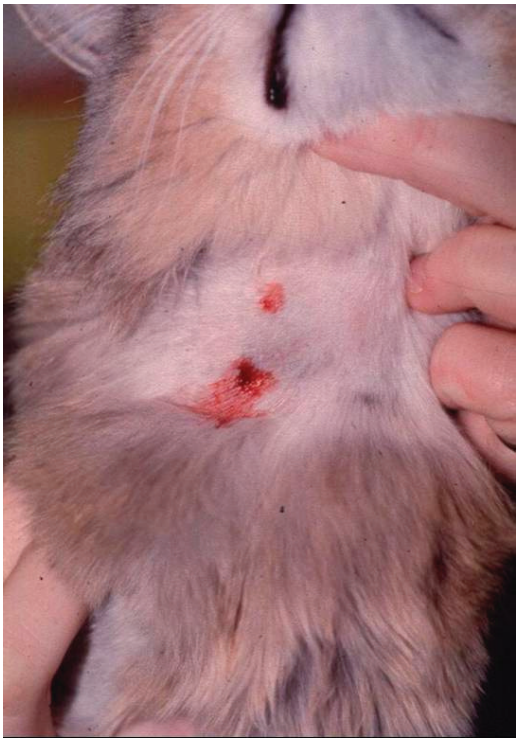

Figure 60-2. Cat with severe primary immune-mediated thrombocytopenia. Persistent oozing of blood from a site of recent venipuncture was noted in this cat with primary IMT.

Etiology

The causes of thrombocytopenia in cats can be divided into four major pathophysiological categories (Table 60-1): decreased production of platelets, increased utilization of platelets, increased destruction of platelets, and sequestration of platelets.

Decreased Production of Platelets

Decreased thrombopoiesis is reported to be the most common cause of feline thrombocytopenia.[1] Decreased thrombopoiesis is caused almost invariably by diseases primarily affecting the bone marrow. Very uncommonly, only platelet precursors such as megakaryoblasts and megakaryocytes are affected selectively in marrow disorders, particularly in early estrogen toxicity and immune-mediated diseases such as megakaryocyte aplasia; however, other cell lines usually are also involved, which typically results in pancytopenia.[1,11-13] Any generalized marrow disorder has the potential to cause thrombocytopenia. Retroviral infections (feline leukemia virus [FeLV] and feline immunodeficiency virus [FIV]), cytotoxic drugs, aplastic anemia, myelodysplasia, myelofibrosis, and marrow histoplasmosis, for example, all can cause thrombocytopenia (Figure 60-3).[1,2,11-17] Neoplasia of the marrow, such as lymphoma and the leukemias, also can cause thrombocytopenia.[1]

Increased Utilization of Platelets

Consumptive coagulopathies such as disseminated intravascular coagulation (DIC) and thromboembolic disease can cause thrombocytopenia in cats because platelets are consumed during the excessive formation of fibrin clots. DIC or throm-

Table 60-1 | **Potential Causes of Thrombocytopenia in Cats**

DECREASED PLATELET PRODUCTION
Marrow Disorders
Retroviral infection
Feline leukemia virus*
Feline immunodeficiency virus*
Feline panleukopenia virus*
Cytauxzoonosis*
Aplastic anemia*
Megakaryocyte aplasia
Myelofibrosis*
Myelodysplasia*
Marrow amyloidosis*
Myeloid and lymphoid leukemias*
Marrow lymphoma*
Marrow histoplasmosis*
Chronic rickettsial infection*
Whole body irradiation*
Hyperestrogenism (gonadal tumor)
Myelosuppressive/cytotoxic drugs
Alkylating agents*
Cytosine arabinoside*
Chloramphenicol*
Trimethoprim/sulfa*
Griseofulvin (esp. in FIV+ cats)*
Albendazole*
Estrogens
Ribavarin*
SEQUESTRATION OF PLATELETS
Organomegaly
Splenomegaly*
Hepatomegaly

INCREASED DESTRUCTION OF PLATELETS
Primary (autoimmune) IMT*
Secondary IMT
Medications
Penicillins
Cephalosporins
Sulfonamide*
Anticonvulsants
Methimazole/carbamazole*
Propylthiouracil*
Modified-live vaccines
Neoplasia
Myeloproliferative disease*
Lymphoma*
Infection
Feline leukemia virus*
Rickettsial diseases*
*Mycoplasma haemofelis**
Multisystem immune disorders
Evan's syndrome*
Systemic lupus erythematosus*
Alloimmune platelet destruction
Platelet transfusion reactions
Neonatal alloimmune thrombocytopenia
INCREASED UTILIZATION OF PLATELETS
Consumptive coagulopathies such as DIC
Neoplasia (especially lymphoma)*
Infection (especially FIP, sepsis)*
Cardiac disease*
Liver disease*
Shock*
Vasculitis*
Hemorrhage (mild thrombocytopenia only)*

*Diseases that are either published causes of thrombocytopenia in cats or have been reasonably well documented based on clinical case experience.

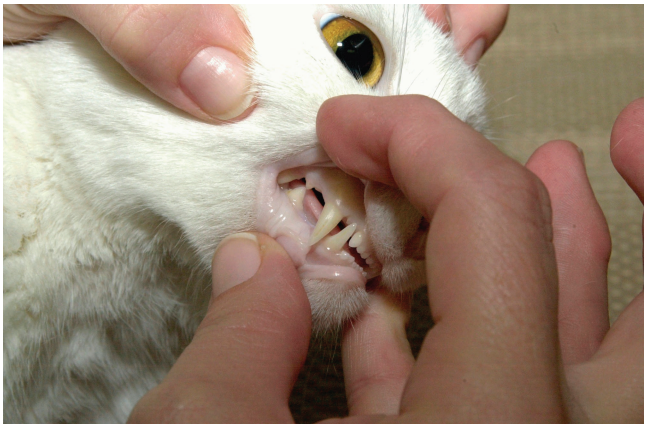

Figure 60-3. Cat with feline leukemia virus infection: pale mucous membranes due to severe non-regenerative anemia. This cat had FeLV-associated aplastic anemia with associated pancytopenia (marked anemia, thrombocytopenia, and neutropenia). Despite profound thrombocytopenia (platelet count less than 10×10^9/L), the cat was showing no clinical signs consistent with a bleeding disorder and tolerated bone marrow aspiration and biopsy without excessive bleeding.

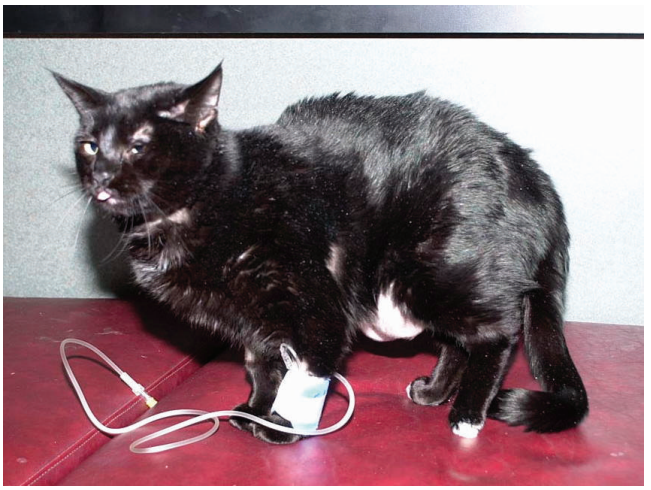

Figure 60-4. Cat with bacterial endocarditis and aortic thromboembolism. This cat presented with an acute saddle thrombus affecting both back legs. At the time of presentation, the cat's platelet count was 91×10^9/L, presumably as a result of a consumptive coagulopathy associated with thrombus formation. Three days later, the clot had dissolved, the cat had regained hind leg function, and the platelet count had risen to normal range.

boembolic disorders in cats occur secondarily to a wide range of diseases including neoplasia (especially lymphosarcoma and hemangiosarcoma), infections (especially feline infectious peritonitis), hepatopathy, cardiac disease, and shock (Figure 60-4)[1,9,10] (see Chapters 37 and 58). In addition to causing thrombocytopenia, consumptive coagulopathies often are associated with platelet dysfunction and abnormal secondary hemostasis because the breakdown products caused by fibrinolysis (fibrin degradation products) impair the function of platelets and clotting factors, and because clotting factors are consumed along with platelets.[10]

Hemorrhage also is sometimes reported as a cause of thrombocytopenia. However, because the marrow can increase thrombopoiesis rapidly in response to platelet loss, and because the spleen contains a reserve of platelets that can be released on demand, as much as 75 per cent of the total blood volume must be lost acutely before significant thrombocytopenia is seen. Acute blood loss of this magnitude leads to death of the cat resulting from shock long before thrombocytopenia becomes severe. Therefore, very low platelet counts (fewer than 50×10^9 platelets/L) in a bleeding cat are far more likely to be the cause rather than the effect of the hemorrhage.

Increased Destruction of Platelets

Immune-mediated thrombocytopenia (IMT), a common cause of increased platelet destruction in dogs, is much rarer in cats.[1,6,9] IMT may be autoimmune (primary) or, more commonly, secondary to drugs, modified-live vaccines, neoplasia (especially myeloproliferative disease), or infectious processes such as FeLV infection or rickettsial diseases.* Drugs that have been implicated in feline IMT include penicillins, cephalosporins, sulfonamides, anticonvulsants, methimazole, propylthiouracil, and doxorubicin.[9] Primary IMT also has been reported in a small number of cats but appears to be a rare condition.[1,6,9] Clinicians making a diagnosis of primary IMT in a cat should be highly suspicious that, in reality, a secondary cause of IMT has been overlooked. Feline IMT also can occur concurrently with immune-mediated hemolytic anemia (Evan's syndrome) and systemic lupus erythematosus (SLE).[1]

Sequestration of Platelets

Splenomegaly or hepatomegaly in theory can cause thrombocytopenia resulting from an increased organ platelet storage capacity. Thrombocytopenia would, however, be expected to be mild and transient because the marrow would respond quickly by increasing platelet numbers.

Clinical Signs

Spontaneous bleeding is observed frequently with platelet counts of less than 50×10^9/L in human beings and dogs but, in contrast, bleeding occurs rarely in cats unless platelet counts fall well below 30×10^9/L.[1] Bleeding in cats with platelet counts of more than 30×10^9/L strongly suggests the presence of concurrent platelet function defects or disorders of secondary hemostasis. Clinical signs associated with thrombocytopenia are typical of defective primary hemostasis and include petechial and ecchymotic hemorrhages, ocular hemorrhage, epistaxis, and gastrointestinal and urogenital bleeding.[6]

Diagnosis

Sample Handling

Compared with other species, feline platelets tend to be hyperaggregable. Platelet aggregation (clumping) in vitro often is triggered by venipuncture and the subsequent handling and storage of feline platelets. Because clumping is a common cause of erroneously low platelet counts in cats, venipuncture should be minimally traumatic, and samples should be processed as soon after collection as possible. Refrigeration of samples also increases platelet clumping and should be avoided before platelet counts. The jugular vein is the preferred site of blood collection in cats because the slower flows associated with the use of smaller limb veins also predispose to platelet clumping although, in cats with suspected severe hemostatic defects, the jugular vein should be compressed carefully for at least 5 minutes after collection and then covered with a light compressive bandage. Ideally, samples should be taken from vessels that have not been traumatized by previous venipuncture and should not be collected through venous catheters. To further minimize the chances of platelet activation and clumping post collection, a two-syringe collection technique also has been suggested, in which the first few milliliters of blood collected through a needle are discarded before a second syringe is attached for sample collection. The process of interchanging syringes on a needle inserted in the vein of an awake cat is, however, usually not feasible in clinical practice.

The degree of platelet clumping also may be affected by anticoagulants. EDTA, the most common anticoagulant used by veterinarians, predisposes feline blood samples to platelet clumping.[2,3,20,21] EDTA-dependent pseudothrombocytopenia in human beings is a relatively common phenomenon, in which marked platelet clumping occurs in the presence of EDTA anticoagulant, which leads to an underestimation of platelet numbers by hematology analyzers.[22] Platelet clumping in human EDTA-dependent pseudothrombocytopenia is caused by antiplatelet antibodies in patient serum, antibodies that bind only to platelets previously exposed to EDTA.[22] Because the presence of EDTA is necessary to trigger platelet clumping, this phenomenon does not directly affect patient health but causes a dramatic decrease in analyzer platelet counts once the blood is exposed to anticoagulant. EDTA-dependent pseudothrombocytopenia has been well documented in horses,[23] and a similar phenomenon appears common in cats.[2,3,21,24] Up to approximately 50 per cent of feline blood samples collected in EDTA experience a mild to marked artifactual reduction in analyzer platelet counts.[2,3,20,21] This artifactual reduction in platelet counts is well documented to occur after sample storage for a relatively short period of time (about 6 hours), but in individual cats can occur much more rapidly.[3,24] Thorough and vigorous mixing of EDTA samples immediately before analysis may help to break up platelet aggregates to some extent, but even aggressive "vortex mixing" has been shown to be only partially effective at eliminating erroneously low analyzer platelet counts in cats.[25]

Sodium citrate is not as likely to cause clumping in cats and may be the routinely available anticoagulant of choice for feline platelet counts.[3] Sodium citrate does not, however, eliminate clumping altogether and, because a fixed and relatively large volume of anticoagulant is needed, may cause a mild dilutional decrease in platelet numbers.[3] Experimentally, exposure of platelets to prostaglandin E_1, an inhibitor of platelet function, also has been shown to improve the accuracy of feline analyzer platelet counts by reducing platelet clumping.[26] A commercial citrate-based anticoagulant containing a mixture of the platelet inhibitors theophylline, adenosine, and dipyridamole (CTAD, Becton Dickinson Diagnostics, Franklin Lakes, NJ), developed for human platelet studies, has a similar beneficial effect on feline analyzer platelet counts.[21] Spiking EDTA tubes with a

*References 1,9,15,16,18,19.

small amount of the antibiotic kanamycin also eliminates erroneous decreases in analyzer platelet counts in cats effectively,[24] a poorly understood phenomenon well documented in human EDTA-dependent pseudothrombocytopenia. However, routine protocols for the addition of prostaglandin E_1, CTAD, or kanamycin to feline blood samples have not been established for clinical practice.

Methods of Estimating Platelet Number

Feline platelet numbers may be estimated by hematology analyzers, by hemacytometer, or by examination of a stained blood smear. Most hematology analyzers available in the veterinary field use electronic resistance (impedance) or more recent laser technology to size and then count blood cells, or quantitative buffy coat (QBC) methodology, in which centrifugation is used to separate cell types into layers based on cell density for subsequent analysis. The technology underlying hematology analyzers is progressing at a staggering rate, and these machines are far more sophisticated than they were a decade ago.

The basic premise underlying all of these analyzers is, however, still simple: to be accurate, analyzers must be able to differentiate between cell types reliably based primarily on cell size and/or cell density. The accurate counting of platelet numbers in cats unfortunately is one task that no currently available analyzer has mastered completely, a problem largely the result of two features of feline platelets. First, and most important, feline platelets are prone to clumping after collection.[2,20,24] Analyzers typically have difficulty recognizing large platelet clumps and certainly cannot count individual platelets within a clump. Second, compared with other species, feline platelets are relatively large (mean platelet volume in cats is approximately 12 to 15 fl,[4] almost double typical platelet volume in dogs) and feline red cells are small. In some cats, this can lead to a size overlap between platelets and erythrocytes, and platelets therefore can be miscounted as red blood cells. Because platelet clumping and cell size overlap lead to a failure to recognize platelets, the most significant problem associated with feline analyzer platelet counts is a false reporting of thrombocytopenia in a cat with normal platelet numbers.[2,3]

Diagnostic accuracy for feline platelet counts using most standard hematology analyzers is poor, and erroneously low counts are common.[2,3,20] In contrast, because it is rare for hematology analyzers to create significant numbers of platelets erroneously that do not exist, analyzer platelet counts within normal reference ranges typically are reliable. Hematology analyzers therefore still have a valuable role in feline platelet counting: these analyzers are rapid and convenient and, when platelet numbers are reported to be normal, platelet counts usually can be trusted. Genuine thrombocytopenia in cats is uncommon and fictitious thrombocytopenia is common. Veterinarians should assume therefore that until proven otherwise, an unexpectedly low feline platelet count reported by a hematology analyzer is most likely to be an artifact and that platelet numbers then must be evaluated using some other means.

Arguably the most accurate method for platelet number determination in cats is manually with use of a hemacytometer. The use of hemacytometer counts has, however, not been adopted by many veterinary practices, probably because practitioners consider the technique to be laborious and time consuming. With experience, however, hemacytometer counts actually are simple to perform and relatively reliable and represent an excellent means of reevaluating dubious analyzer platelet count results.[3,20] Feline platelet counts also can be estimated reliably via the light microscopic examination of a stained blood smear.[2,27] To minimize platelet clumping, smears should be prepared and air-dried within minutes of sample collection into anticoagulant and then stained with a standard hematological stain. The number of platelets per oil immersion field (×1000 power) in the monolayer area of the smear is counted. Multiple fields should be examined and the average number of platelets per field determined and multiplied by a factor of 20 to obtain an estimated platelet count ($\times 10^9$/L).[27] The entire smear should be screened first at low power to ensure no platelet clumps are present, which could lead to an artificially low platelet count. The presence of many platelet clumps on a smear usually is consistent with a normal platelet count, even if individual platelets cannot be counted.[27] Examination of a stained blood smear also provides a means of recognizing shift or stress platelets (megathrombocytes), large platelets highly suggestive of an increased marrow production and release of platelets. Shift platelets are defined as platelets at least as large as nearby erythrocytes.

Because feline platelets tend to clump during the transportation process and hematology analyzers can give falsely low platelet counts in cats, a definitive diagnosis of thrombocytopenia often cannot be made reliably from a whole blood sample submitted to an outside clinical pathology laboratory. Feline practitioners therefore should submit a fresh air-dried blood smear routinely along with an anticoagulated blood sample. The clinical pathology laboratory then can perform an estimate of platelet numbers from the smear to determine if analyzer results are real or erroneous.

Further Diagnostic Testing

Diagnostic tests often indicated in cats with confirmed significant thrombocytopenia include those detailed below.

Complete Routine Hematology

Examination of a blood smear may provide clues as to the specific cause of thrombocytopenia in cats. Bone marrow disorders that result in thrombocytopenia often cause concurrent nonregenerative anemia and leukopenia (particularly neutropenia).[11-13] Fragmented red cells (schistocytes) on a smear from a thrombocytopenic cat suggest possible DIC. Rarely, the presence of typical morulae in blood cells may indicate the presence of rickettsial disease.[28]

Hemostatic Parameters

Evaluation of a profile of hemostatic indices, such as prothrombin time (PT), activated partial thromboplastin time (PTT), and fibrin degradation products (FDP) or D-dimer, is needed to confirm a diagnosis of a "complex" hemostatic disorder such as DIC, a relatively common cause of thrombocytopenia in cats.[10] Cats with consumptive coagulopathies such as DIC often have multiple hematological and hemostatic abnormalities accompanying a low platelet count, including schistocytosis, prolonged PT and PTT, and elevated FDP and D-dimer.[1,9,10] However, even in the presence of multiple typical hemostatic test results, a diagnosis of DIC cannot truly be

established unless the presence also is confirmed of an underlying disease known to cause consumptive coagulopathies.

Testing for Infectious Diseases

Thrombocytopenia in cats is associated commonly with infectious diseases, especially FeLV.[1] FeLV testing, therefore, should be performed in all thrombocytopenic cats. Other infectious agents that may be associated with thrombocytopenia less commonly in cats (usually in combination with other characteristic clinical signs and laboratory abnormalities) include FIV,[1,15,16] FIP virus,[1,10] *Mycoplasma haemofelis*[1] (see Chapter 63), and *Toxoplasma gondii*.[1] *Ehrlichia*-like organisms have been reported to be the suspected cause of thrombocytopenia in cats, typically in combination with other clinical signs comparable to ehrlichiosis in dogs, including fever, polyarthritis, neutropenia, and anemia.[18,19] Infected cats may cross-react antibody-positive for a number of rickettsial species, including *Ehrlichia canis* and *Neorickettsia risticii* (known until recently as *Ehrlichia risticii*).[18,29] Polymerase chain reaction (PCR) tests for rickettsial organisms also may be positive in blood samples from affected cats: *E. canis* and *Anaplasma phagocytophilum* (known previously as *Ehrlichia equi*) have been detected in cats using PCR.[19,28]

Diagnostic Imaging

Because thrombocytopenia in cats can occur secondarily to neoplasia, thoracic and abdominal radiography and abdominal ultrasonography (looking for masses, lymphadenopathy, or organomegaly) often are indicated in cats with unexplained low platelet counts.

Bone Marrow Evaluation

Bone marrow analysis (aspiration and/or core biopsy) allows evaluation of megakaryocytes and other platelet progenitor cells and typically is necessary to determine the cause of thrombocytopenia in cats with primary failure of marrow platelet production. Marrow analysis is indicated particularly for cats with pancytopenia.[11-13] Many of the diverse range of feline marrow diseases that can cause thrombocytopenia can be diagnosed only by analysis of bone marrow specimens. Marrow collection is relatively safe in thrombocytopenic cats and typically is not associated with excessive bleeding. Marrow analysis, however, usually is not indicated if adequate thrombopoiesis already has been suggested by the presence of shift platelets on examination of a blood smear. Immunofluorescent or immunoperoxidase labeling of marrow cellular elements can be performed to document immune-mediated destruction of megakaryocytes by the demonstration of antimegakaryocytic antibody, although the diagnostic reliability of such procedures has not been validated. Immunofluorescent assay (IFA) of bone marrow smears also may be used to diagnose challenging cases of FeLV, in which the presence of organism appears restricted predominantly to the marrow. PCR testing for FeLV and FIV also can be performed on marrow samples.

Immunological Testing

Confirmation of the diagnosis of feline primary IMT is difficult. Immunological tests for antiplatelet antibody are either unreliable or not readily available for cats, and a diagnosis of IMT often is made in retrospect after an appropriate response to immunosuppressive therapy is observed. However, immunosuppressive agents should be initiated only after other much more common causes of thrombocytopenia in cats (such as marrow diseases and DIC) have been excluded carefully by thorough diagnostic testing. In the rare cat with suspected concurrent IMT and immune-mediated hemolytic anemia or SLE, further immunological assessment via Coombs' or antinuclear antibody testing may be indicated.

Reticulated Platelets

Reticulated platelets are newly released immature platelets that contain RNA that stains positive with the dye thiazole orange. The marrow is believed to produce these platelets in increased numbers in response to diseases that cause enhanced thrombopoiesis. Feline thiazole orange–positive platelets can be counted rapidly and accurately via flow cytometry.[17] In theory, detection of increased numbers of reticulated platelets suggests that failure of marrow production is not the cause of thrombocytopenia. Reticulated platelet counts, however, have not been well validated in cats and have not attained common usage.

Treatment

Cats with mild to moderate thrombocytopenia are not at significant risk of bleeding, and clinicians therefore can take time to investigate potential underlying causes of a low platelet count carefully and to institute specific treatments of those causes. Cats with marked thrombocytopenia, in contrast, should be considered at immediate risk for life-threatening hemorrhage, even if they appear to be clinically stable. Appropriate supportive and specific treatment measures should be instituted immediately.

Supportive Treatment

Regardless of the cause of thrombocytopenia, platelet counts rarely rise significantly in the first few days of disease-specific treatment. To prevent the patient with marked thrombocytopenia from succumbing to a hemorrhagic episode before platelet numbers rise to adequate levels, careful supportive care is essential during the initial treatment phase. Methods for minimizing hemorrhage include strict rest, gentle handling, and avoidance of elective surgery and other procedures that cause vascular trauma, such as intramuscular injections. Drugs that induce platelet dysfunction, such as nonsteroidal antiinflammatory drugs, also should be avoided. Cats can be hospitalized, and sedated if very active or fractious. At least outdoor cats should be moved indoors. Blood collections should be planned carefully and should be completely justifiable to minimize unnecessary venous trauma, small-bore needles and catheters should be used whenever possible, and veins should be compressed or bandaged for a sustained period after venipuncture. Major body cavity hemorrhage is unlikely in cats with thrombocytopenia but, when present, typically does not require drainage. Thoracocentesis or abdominocentesis may exacerbate bleeding and usually is best avoided unless dyspnea or abdominal distention is severe or life threatening.

Emergency volume or RBC support with fluids (crystalloids or colloids) or blood products is indicated in thrombocytopenic

cats with acute blood loss and associated hypovolemia or anemia. Acute episodes of hypovolemic shock secondary to blood loss may be treated most simply with crystalloids such as 0.9 per cent saline or with synthetic colloids such as dextrans or hetastarch, although synthetic colloids should be used with caution because they may exacerbate hemostatic defects. In cats with bleeding disorders, blood products are used either to address anemia and hypovolemia or to replace missing platelets and/or clotting factors. Although stored whole blood, packed red cells or, when available, bovine purified polymerized hemoglobin (Oxyglobin, Biopure Corporation, Cambridge, MA) may be sufficient to treat anemia and hypovolemia, the replacement of specific hemostatic components requires transfusion with either fresh whole blood or specialty blood products derived from fresh blood such as platelet-rich plasma, platelet concentrate, fresh plasma, fresh frozen plasma, or cryoprecipitate. Many of these specialty feline blood products are, however, often not provided by commercial blood banks, and cannot be produced easily in practice. Practitioners therefore often must resort to the use of whole blood collected freshly from local feline donors as a source of a combination of red cells, platelets, and plasma.

Platelet transfusion, either in the form of fresh whole blood or as specific platelet products, often is minimally effective in thrombocytopenic cats, because an underlying platelet consumptive or destructive process leads to extremely rapid loss of transfused platelets.[30] In such circumstances, practitioners should rely on specific treatment modalities (such as steroids or tetracyclines) to increase platelet numbers and, until thrombocytopenia resolves, use fluids or blood as needed to support volume and red cell numbers rather than resorting to platelet transfusions. Platelet transfusion may be slightly more effective, at least for a few days, in cats with thrombocytopenia resulting from marrow failure.[30] Because cats often can tolerate marked thrombocytopenia without excessive bleeding, a very low platelet count of about 5×10^9/L has been suggested as a "transfusion trigger point" at which fresh whole blood or other platelet products should be administered.[30] Because thrombocytopenia this extreme is encountered rarely in cats in clinical situations, specific transfusion of feline platelet products tends to be an uncommon to rare event.[30]

Autotransfusion, the readministration of blood drained from a body cavity, provides volume and red cells but not clotting factors or platelets. Blood obtained from a body cavity must be run through a filter to remove blood clots before transfusion and should not be used in cases with a risk of contamination with bacteria, intestinal luminal contents, or (arguably) neoplastic cells.

Specific Treatment

Appropriate specific treatment of the causes of thrombocytopenia is dependent on obtaining a correct diagnosis. Rickettsial infections, for example, are treated with oral tetracycline or doxycycline,[18,29] marrow lymphoproliferative disease is treated with chemotherapy, aplastic anemia and myelofibrosis may respond to immunosuppressive therapy, and drug-induced myelosuppression may resolve once causative medications are tapered or discontinued.

Because most cases of feline IMT are secondary to an underlying disease, appropriate treatment depends on identification and removal or treatment of potential triggers such as medications, infectious diseases, or neoplasia. Immunosuppressive therapy is indicated in cats with primary IMT and in cats with secondary IMT that do not respond rapidly to removal of underlying causes. Cats do not tolerate immunosuppressive agents as well as dogs. Often, formulation of standard dosage forms to a size safe for cats is difficult. Fortunately, cats are remarkably tolerant of long-term high doses of glucocorticoids, and most cats with IMT respond to steroids alone. For this reason, other immunosuppressive agents such as cyclophosphamide or cyclosporine rarely are needed.

Identification and treatment (if possible) of underlying disorders are the cornerstones of management of DIC. In the meantime, transfusion with fresh whole blood or fresh frozen plasma to replace depleted clotting factors and antithrombin should be considered in cats with DIC, particularly if the patient is bleeding actively. Heparin inhibits several factors within the clotting cascade and may prevent ongoing consumption of platelets and clotting factors in cats with DIC. In cats with active DIC, heparin is safe and effective only if clotting factor and antithrombin levels are restored by concurrent transfusion of fresh plasma or whole blood.

THROMBOCYTOSIS

Thrombocytosis (platelet counts significantly greater than 800×10^9/L) is relatively uncommon in cats. Probably the most common cause of increased platelet numbers in cats is secondary thrombocytosis, a phenomenon observed occasionally in association with a wide variety of physiological and disease processes. Secondary thrombocytosis usually causes only mild to moderate transient increases in platelet number, and the thrombocytosis itself typically is asymptomatic. Platelet function in cats with secondary thrombocytosis usually is normal, and affected animals therefore are not susceptible to hemorrhage or thrombosis.

Thrombocytosis associated with many different etiologies can be included loosely under the diagnostic umbrella of "secondary thrombocytosis." Transient physiological thrombocytosis can be observed occasionally, possibly as a result of epinephrine-induced splenic contraction in excited cats and in cats with acute blood loss. More sustained thrombocytosis also is seen as a predictable sequela to splenectomy. So-called reactive thrombocytosis, a sustained rise in platelet numbers that has not been well explained in any species, also can be seen with iron deficiency, infectious and inflammatory diseases, neoplasia, and glucocorticoid excess. Thrombocytosis also may be drug induced: the administration of vinca alkaloids such as vincristine to human beings and dogs with normal platelet counts often induces a transient moderate rise in platelet numbers, a response that also has been observed anecdotally in the occasional cat receiving vincristine chemotherapy. Idiopathic mild to moderate elevations in platelet number of no detectable clinical significance are observed occasionally in apparently healthy cats.

Very high platelet counts (often far exceeding $1{,}000 \times 10^9$/L) can be seen with primary platelet leukemias such as primary (essential) thrombocythemia and megakaryoblastic or megakaryocytic leukemias.[31,32] Essential thrombocythemia is a leukemia of mature platelets, whereas megakaryoblastic or megakaryocytic leukemias often feature high circulating numbers of platelet precursors and immature, large and bizarre platelets.[31] Both conditions can be associated with FeLV

infection. Essential thrombocythemia is a rare myeloproliferative disorder characterized by the uncontrolled neoplastic production of platelets.[32] Platelet numbers in cats with essential thrombocythemia often are extremely elevated, whereas other cell lines typically are unaffected. Megakaryoblastic or megakaryocytic leukemias also can cause marked increases in circulating platelet number but often are associated also with decreases in numbers of other circulating blood cells resulting from extensive bone marrow involvement and myelosuppression.

Thrombocytosis sometimes is observed in association with other myeloproliferative disorders such as polycythemia vera and myelogenous leukemia, and arguably may represent neoplastic proliferation of more than one cell line. Interestingly, one of the most common presenting complaints associated with the platelet leukemias is hemorrhage, probably resulting from defective platelet function.[32] Severe thrombocytosis also can predispose theoretically to thromboembolic disorders and organ infarction, although such complications are reported rarely. Marked thrombocytosis can cause pseudohyperkalemia, an in vitro artifact seen in clotted (serum) samples and caused by the release of potassium from platelets during the post-collection clotting process.

Treatment of platelet leukemias has been reported rarely in cats.[32] Based on experiences in other species, potential chemotherapeutic agents include hydroxyurea and alkylating agents such as melphalan.

THROMBOCYTOPATHIES

Clinically significant disorders of platelet function (thrombocytopathies, also known as thrombopathias) are uncommon to rare in cats. Thrombocytopathies may be hereditary or acquired. Hereditary disorders that cause impaired platelet function are uncommon in cats and include von Willebrand's disease (vWD), collagen deficiency diseases, and Chédiak-Higashi syndrome (see Chapter 61). Hereditary platelet disorders, when present, can be relatively severe and may be associated with spontaneous bleeding at a young age.[7] In comparison, although acquired platelet dysfunction is more common than hereditary thrombocytopathies in cats, acquired function defects tend to be milder, and episodes of spontaneous hemorrhage are rare. Bleeding, however, may be excessive after relatively invasive procedures such as surgery or tissue biopsies. Potential causes of acquired platelet dysfunction in cats include renal failure, liver disease, immune-mediated thrombocytopenia (antiplatelet antibodies may impair platelet function), neoplasia, and numerous medications (most notably nonsteroidal antiinflammatory agents such as aspirin).

Defective platelet function should be suspected in cats with normal platelet counts and a history and clinical signs consistent with a disorder of primary hemostasis. The careful collection of a detailed history is essential for the diagnostic investigation of cats with suspected disorders of platelet dysfunction. Middle-age and older cats known to have survived previous surgery or other traumatic events without significant bleeding are unlikely to have a hereditary defect in platelet function. Questioning regarding recent drug history should be directed carefully, because owners may fail to recognize that medications such as nonsteroidal antiinflammatory drugs are worthy of mention. Clinical signs associated with severe thrombocytopathies are typical of those seen with other more common disorders of primary hemostasis such as thrombocytopenia.

A number of specialized in vitro tests of platelet function have been evaluated clinically or experimentally in cats including, most commonly, platelet aggregometry, which tests the ability of platelets to aggregate in response to various agonists. Platelet aggregometry, although it has been used extensively for clinical research purposes in cats,[7,33-36] is available uncommonly for the routine clinical evaluation of platelet disorders in cats. Newer "in-house" platelet function analyzers, in particular the PFA-100 (Dade Behring Inc., Deerfield, IL), may become more available for routine clinical use, but the considerable expense of such analyzers probably will limit their use to large centers with a specialist interest in hemostasis. Unfortunately, because most specialized in vitro platelet function tests are run on blood samples collected freshly from the patient, such tests are not feasible as "send out" tests for local feline practitioners. Therefore, practitioners who wish to evaluate platelet function usually are limited to simple in vivo tests of primary hemostasis such as the buccal mucosa bleeding time BMBT.

The BMBT allows practitioners to perform a simple in vivo evaluation of primary hemostasis in cats.[33,37] With this procedure, a specialized spring-loaded device (Triplett, Helena Laboratories, Beaumont, TX; Surgicutt, International Technidyne Corporation, Edison, NJ) is used to make a small, standardized incision in the buccal mucosa, and the time taken for the combination of vessel and platelet interactions to seal this vascular defect is measured (Figure 60-5). The BMBT evaluates all aspects of primary hemostasis and has the potential therefore to be prolonged in cats with vascular disorders and cats with

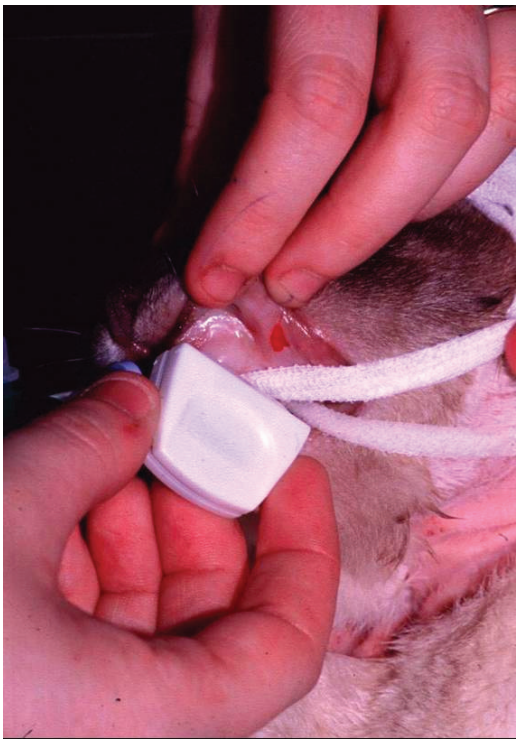

Figure 60-5. Performance of a buccal mucosa bleeding time in an anesthetized cat.

defects in platelet number or function. Performing a BMBT usually requires heavy sedation or anesthesia in cats.[7,37,38] The mean BMBT for cats is about 2 to 4 minutes,[33,37] and a BMBT of more than 4 minutes is highly suggestive of a hemostatic disorder.[7] The BMBT should be performed only in cats with adequate platelet counts, because the test will be predictably prolonged, and thus superfluous, in cats in which marked thrombocytopenia has been diagnosed already. A prolonged BMBT in a cat with adequate platelet numbers is not a specific test of platelet function and suggests the presence of either platelet dysfunction or vessel disorders such as inherited collagen disorders or vasculitis (caused by a wide range of etiologies, including rickettsial diseases and FIP). The cuticle bleeding time, in which the time taken for a clipped toe nail to stop bleeding is measured, also has been suggested as an alternative to the BMBT but is not recommended for routine use because of associated discomfort and a lack of test specificity (cuticle bleeding times also may be prolonged with disorders of secondary hemostasis).

Hereditary Thrombocytopathies

vWD is a hemostatic disorder caused by a deficiency of the functional forms of vWF, a circulating glycoprotein. Strictly speaking, vWD is not a true platelet disorder, because the platelets of cats with vWD are anatomically and functionally normal. However, because adequate vWF is required for normal platelet adhesion to damaged vascular surfaces, cats with vWD present as a typical disorder of platelet dysfunction. Compared with dogs, vWD is very uncommon in cats.[8] Plasma levels of vWF can be evaluated as a simple and stable send-out test to confirm a diagnosis of vWD in cats.

Ehlers-Danlos syndrome is an uncommon inherited feline collagen disorder that causes excessive joint laxity, dermal hyperextensibility and fragility, and a mildly increased predisposition to bleeding because of abnormal vessel ultrastructure. Platelet structure and function in cats with collagen disorders is normal and therefore, as with vWD, Ehlers-Danlos syndrome is not a true platelet function disorder. However, because normal subendothelial collagen is necessary for platelet adhesion to damaged vessels, cats with Ehlers-Danlos syndrome can present with a predisposition to bleeding comparable to a typical thrombocytopathy.

True hereditary disorders of platelet function are uncommon to rare in cats compared with other species. The best-described feline hereditary thrombocytopathy is Chédiak-Higashi syndrome.[37-40] (See Chapter 61.) Chédiak-Higashi syndrome is an uncommon autosomal recessive disorder that has been reported in Persian-type cats with pale yellow-green irises and a diluted smoke-blue hair coat.[39,41] The retina of cats with Chédiak-Higashi syndrome often appears reddish-gray and lacks normal tapetal reflectivity: affected cats also may have cataracts and fine nystagmus and may appear light sensitive.[41] Platelets of affected cats lack dense bodies, intracytoplasmic granules that contain serotonin, histamine, and the adenine nucleotides essential for normal platelet metabolism.[40] The cytoplasm of the neutrophils of affected cats also is abnormal and typically contains large eosinophilic lysosomal granules.[39] Detection of these granules within neutrophils on examination of a blood smear confirms the diagnosis of Chédiak-Higashi syndrome (see Figure 61-9). Neutrophil function in cats with Chédiak-Higashi syndrome is impaired, and severely affected cats may have an increased susceptibility to infection.[37] Cats with Chédiak-Higashi syndrome have a markedly prolonged BMBT[37] and can be prone to bleeding as a result of platelet dysfunction,[39,40] particularly after surgery or invasive procedures. Other suspected hereditary thrombocytopathies have also been reported in cats[7] but are not as well described as Chédiak-Higashi syndrome.

Acquired Thrombocytopathies

Numerous acquired disorders in platelet function have been reported in human beings, associated with such conditions as liver disease, uremia, DIC, various neoplasms, dysproteinemias such as the monoclonal gammopathy seen with multiple myeloma, and various drug therapies. Cats appear to be affected by a similar range of acquired platelet function defects to those seen in human beings, although such acquired thrombocytopathies are not as well documented in cats. Medications that have been reported to affect platelet function in many different species include nonsteroidal antiinflammatory drugs, synthetic colloids, penicillins, and a number of sedative and anesthetic agents such as acepromazine, diazepam, ketamine, propofol, and halothane. Experimentally, various human antiplatelet drugs have been shown also to impair platelet function in cats, including clopidogrel[35] and ticlopidine[36] (see Chapter 37).

The supportive treatment of cats with thrombocytopathies is similar to the supportive therapy of cats with severe thrombocytopenia. Acquired thrombocytopathies are best treated, when feasible, by treatment or removal of the underlying cause. In cats with true hereditary or acquired platelet function disorders, fresh whole blood or platelet transfusions may be used to provide sufficient functional platelets to support the patient temporarily through invasive procedures such as surgery or biopsies. Cats with vWD or collagen disorders, in contrast, typically do not respond to platelet transfusions. In cats with vWD, plasma products such as fresh whole blood, fresh plasma, or cryoprecipitate can be used to provide sufficient vWF temporarily to arrest bleeding crises or withstand invasive procedures.

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Chapter 61

INTERPRETING THE LEUKOGRAM

Charles W. Brockus

The leukogram often appears deceptively simple; however, interpretation requires diligence in obtaining evolving pieces of past, present, and potentially future information, then collation of this information into an accurate assessment. The complete blood count (CBC) or hemogram is an essential and fundamental component of the minimum laboratory database used to evaluate animal health. Interpretation of the CBC is most accurate when combined with other information (i.e., signalment, history, physical examination). Information obtained from the CBC is quantitative and qualitative, and represents the present (time of blood collection) status of erythrocytes, platelets, and leukocytes. The leukogram, or white blood cell count (WBC), provides information about leukocytes, which includes granulocytes (neutrophils, eosinophils, and basophils) and mononuclear cells (lymphocytes and monocytes). Some leukogram patterns are observed commonly and interpreted easily, such as the stress or physiologic leukogram, whereas others are rapidly changing mixtures or combinations of physiological responses more difficult to assess. Even if initial leukogram parameters are within reference values, this does not mean the animal necessarily is healthy. Within each data set, physiological responses are observed at one specific point in time (blood collection), and knowledge of the full extent of the particular time point in the disease process often is unknown. Because leukocytes are short-lived in circulation, factors within peripheral circulation can alter leukocyte numbers rapidly. This may necessitate performing multiple CBCs to observe or detect trends that help identify systemic effects of a disease process or establish a diagnosis or prognosis.

Complete interpretation requires assessment of absolute numbers of leukocytes and microscopic examination of leukocyte morphology. Both are essential in evaluation of the leukogram. Many laboratories include relative percentages (relative quantities) and absolute quantities (absolute numbers), but relative percentages often are inaccurate (e.g., percentages within reference values with abnormal total numbers). Only absolute numbers should be used for interpretative purposes because these reflect total numbers of individual cell types present.

Significant concern has arisen since on-site hematology analyzers have become commonplace in veterinary practices. Although many veterinarians use these analyzers effectively, some rely on these analyzers without performing microscopic examination of blood smears, which results in "incomplete leukograms" or "incomplete CBCs." Leukocyte counts and classification by some machines are good, whereas others only differentiate granulocytic from mononuclear cells. Therefore microscopic examinations of blood smears are essential for proper and complete leukogram interpretation.

Combining the reported leukogram information with signalment, historical information, and complete physical examination is exceedingly important. Signalment can be informative as to possible abnormalities or anomalies observed in the leukogram, such as Birman cat neutrophil granulation anomaly or Chédiak-Higashi syndrome (see below). Historical information is absolutely necessary to determine the animal's travel history, exposure to toxins, activity changes, behavioral changes, weight gain or loss, or if any medications have been administered (e.g., antibiotics, corticosteroids, nonsteroidal antiinflammatory drugs [NSAIDs]), which may mask physical signs and potentially alter laboratory data. Physical examination may reveal a mass, abscess, painful area, or other information leading to a specific diagnosis or assist with leukogram interpretation.

Leukogram interpretation often is not a straightforward, simple, one-time process, because many things may alter the leukogram simultaneously. For example, a stress response can decrease the lymphocyte count, whereas antigenic responses can increase the lymphocyte count (e.g., vaccination or infectious organisms). Such counteracting physiological processes may occur concurrently and produce a "within reference values" lymphocyte count. Therefore many instances arise where "cookbook" interpretation is insufficient, and integration of all available information, along with a repeat leukogram, is necessary for accuracy. Occasionally, a bone marrow aspirate may be necessary for complete evaluation.

LABORATORY DATA INFORMATION

Although veterinarians use human laboratories frequently as their only source of laboratory data results, good veterinary laboratories usually provide more accurate information and often have a veterinary clinical pathologist available for consultation.

Microscopically, morphological differences in leukocytes exist between species. Occasionally, medical technicians at human laboratories are not familiar with leukocyte differences, which results in reports and interpretation of the leukogram that often are inaccurate because of inappropriate leukocyte stage or type identification (i.e., feline band neutrophil and basophil identification). Depending on the laboratory, this may or may not be a problem, and asking a veterinary clinical pathologist to review laboratory results obtained from another laboratory may lead to inaccurate interpretations.

One primary goal is to ensure accurate data are obtained from the laboratory or in-house analyzer. Laboratories that generate their own species-specific reference intervals or reference values produce results far superior to laboratories that use published book values. Producing accurate in-house reference values is costly and requires 100 to 200 apparently healthy animal blood specimens. Additionally, reference intervals vary with breed, age, gender, geographical location, environment, nutrition, lab reagents used, lab technicians, and lab equipment used. Even if a reagent is changed for a specific parameter, a new and possibly different reference interval will be determined for that new reagent. High-quality laboratories also produce reference intervals using animals within their geographical area. Questions about the derivation of reference values directed to the laboratory can help with identifying a facility with quality data production. Precision and accuracy of reported data are the priorities here, not convenience.

When interpreting differential cell counts for leukocytes normally present in numbers less than 10 per cent of the total WBC, such as eosinophils, basophils, or monocytes, producing reference intervals for these cell types is influenced by the fact they do not follow a Gaussian distribution (bell-shaped curve) in healthy animals. In non-Gaussian distributions of leukocytes, cell numbers are commonly "skewed" toward zero, meaning most healthy animals tested have 0 or very low cell counts with only occasional counts being high. Therefore when reference intervals are established as 0 to 750/µL, these intervals are "calculated" to include 95 per cent of the sampled "healthy" animals tested. Because the vast majority of low percentage cells are absent or low, reference intervals will be skewed toward the lower limit (0/µL). The upper limit number (750/µL) actually will be lower than the few "healthy" counts sampled that are high, approaching twice the upper limit. As a result, mild increases in cell types commonly present in low numbers (e.g., eosinophils) can lead to overinterpretation.

BLOOD COLLECTION

Peripheral blood specimens typically are collected in ethylenediamine tetracetic acid (EDTA) anticoagulant blood collection tubes (purple rubber stopper), identified properly, and stored at 4° C before shipping. Shipment of EDTA blood specimens to a laboratory for analysis may occur within hours or potentially require 1 to several days. Numerous degenerative cellular changes take place within hours after collection, including nuclear hypersegmentation, nuclear swelling, pyknosis, and/or cytoplasmic vacuolization. As a result, cell identification often is not possible, or alterations may be interpreted erroneously as toxic changes.[1] Also, these cells are more delicate and tend to rupture easily during preparation of blood smears, which produces basket cells. If more than 10 per cent of nucleated cells are ruptured, the leukocyte count is invalid.[1] Therefore well-prepared blood smears made at the time of sample collection are an essential part of specimen preparation. At least two air-dried, unstained slides should be submitted with each EDTA blood specimen. Slides must be protected from exposure to formaldehyde fumes because these fumes alter specimen-staining characteristics. Slides also must be protected from moisture (cold packs), refrigeration, and flies.

PHYSIOLOGIC LEUKOGRAM

The physiologic leukogram is a transient, nonpathological, variable rise in total leukocyte numbers. Characteristics of this pattern are associated with the systemic effects of epinephrine release as a component of the "fight or flight" response (fear, excitement, or sudden exercise), in which the neutrophil and lymphocyte counts increase because of increases in blood pressure, heart rate, and blood flow.[1,2] This is a "pseudoneutrophilia" that occurs because of abrupt mobilization of the marginating neutrophil pool (MNP), which becomes redistributed into the circulating neutrophil pool (CNP) and causes a transient increase in the total blood neutrophil pool (TBNP)[1,2]:

$$MNP + CNP = TBNP$$

The MNP in cats is substantial, 75 per cent of the TBNP and, as a result, redistribution will produce a pronounced neutrophilia.[1,2] Up to a threefold to fourfold increase in absolute neutrophil counts with an absence of a left shift theoretically could occur in cats because of redistribution of their large MNP.[2,3] A concomitant lymphocytosis also may be observed in cats.

This response is observed most commonly in young, healthy cats when exposed to situations in which they become extremely frightened or excited, including venipuncture, restraint, and/or handling.[1,2] The leukogram associated with these situations is variable but typically is a mild to moderate leukocytosis with reported total leukocyte counts approaching 40,000/µL. Commonly, a mild to moderate mature neutrophilia with counts between 8,000 and 15,000/µL[1] occurs, with absolute neutrophil counts reported exceeding 39,000/µL[2], and concomitant absolute lymphocyte counts between 8,000 and 20,000/µL[1], rarely reaching 36,000/µL.[1,2] Occasionally, lymphocytosis is of greater magnitude than the neutrophilia.[1-3] Lymphocytosis is thought to occur as a result of redistribution of lymphocytes between peripheral blood, lymphoid organs, and lymphatics.[1,2] Changes within the leukogram are immediate and short-lived and last approximately 20 to 30 minutes.[1,2] Concurrent increases in serum glucose, blood pressure, heart rate, and packed cell volume are findings consistent with and supportive of physiologic leukocytosis.[1,3] Rechecking the leukogram within hours after identification of such physiological changes may help distinguish a nonpathological from a pathological leukogram pattern (e.g., lymphoma or lymphocytic leukemia).[3]

STRESS LEUKOGRAM

The typical pattern associated with a corticosteroid-induced leukocytosis response is a mild to moderate leukocytosis with a mature neutrophilia, lymphopenia, eosinopenia, and monocytosis, referred to as a "stress leukogram."[1,2] This pattern occurs as a result of endogenous (pain, high and low body temperatures) release or exogenous administration of

corticosteroids.[1,2] This response is observed less frequently in cats when compared with dogs.[2] Also, neutrophilia is observed but a monocytosis is inconsistent in cats.[1,2] Total WBC varies but ranges commonly from 15,000 to 25,000/µL with extreme cases up to 30,000/µL.[2] Band neutrophils are infrequent unless the mature segmented neutrophil pool has been depleted.[2] Mechanisms causing a stress neutrophilia include decreased emigration from peripheral blood to tissues, increased blood transit time, a shift from MNP to CNP, stimulation of granulopoiesis (chronic administration of corticosteroids), and increased marrow release.[1,2]

Route of administration and dose of corticosteroids affect the magnitude of response.[2] Response to short-acting exogenous corticosteroid (prednisolone) administration occurs within hours and peaks at 4 to 8 hours, with leukocyte counts returning to reference values within 24 to 48 hours after a single injection.[1-3] With termination of chronic steroid therapy, total leukocyte counts may take several days to more than a week to normalize.[2,3] After cessation of alternate-day steroid therapy, normalization of leukocyte counts may take a few days but returns to reference values more rapidly than with chronic daily treatment.[3]

Lymphopenia is caused by a redistribution and/or destruction of circulating lymphocytes. Decreased lymphocytes occur as a result of transient sequestration within lymphoid tissues or bone marrow, or lymphocytes are lysed with high exogenous corticosteroid administration.[1,2]

Monocytosis, although not generally observed in cats, is thought to be caused by an increased distribution from the marginating population to circulating population, similar to that for neutrophilia.[1,2]

True eosinopenia is difficult to identify definitively even in a healthy leukogram; therefore, when associated with a stress response, it is still subject to question. Causes of stress eosinopenia include sequestration or margination of eosinophils within microcirculation or tissues, inhibition of release from bone marrow, and possible inducement of apoptosis and inhibition of cytokines that direct eosinophil development and recruitment.[2]

NEUTROPHILS

Normally, neutrophils are the most predominant leukocyte in circulation with a steady homeostasis between loss and production. Complete replacement of all neutrophils occurs approximately 2.5 times each day.[1,2] Neutrophils are assessed by numbers (quantitative) and morphology (qualitative). Alterations from reference value numbers depend on a balance between bone marrow production and release, intravascular distribution, tissue emigration, and tissue demands.[1,2] With increased tissue demands, alterations occur with the homeostatic balance between marrow production, peripheral destruction, emigration, and sequestration of neutrophils. When tissue demands for neutrophils increase, bone marrow storage pool cells are released and the proliferative pool responds by producing more neutrophils. Therefore, with inflammation, a leukocytosis with a primary neutrophilia is present. When a neutrophilia is sustained over a long period of time, this reflects production of neutrophils surpassing their emigration or loss into tissues. If the inflammatory response is marked or acute, storage and proliferative pools within the bone marrow may not be able to respond rapidly, which results in the release of immature neutrophils (bands, metamyelocytes, myelocytes, and myeloblasts).[2] When demand for neutrophils exceeds the capacity of the bone marrow pools and excess immature stages are released into circulation, this is called a "left shift."[1-3] This pattern is characteristic of an inflammatory leukogram. A left shift is recognized when bands and other immature neutrophils are greater than 1000/µL with a normal or elevated total WBC. If neutropenia exists and more than 10 per cent of total blood neutrophils are immature forms, this also is indicative of high tissue demand and considered a left shift.[2] Generally, a left shift is limited to band neutrophils, but earlier stages may appear with chronicity or severity of disease.[1] Patterns associated with the leukogram left shift are categorized as regenerative or degenerative. A regenerative left shift occurs when mature segmented neutrophils outnumber immature neutrophils, which signifies the bone marrow's ability to meet tissue demands from a marked inflammatory response.[1-3] In contrast, a degenerative left shift pattern occurs when immature neutrophils (bands, metamyelocytes, myelocytes, and/or myeloblasts) outnumber circulating mature segmented neutrophils, which indicates an intense inflammatory response, whereby bone marrow cannot provide for tissue demands.[1-3] A degenerative left shift is associated with a guarded to poor prognosis.[1,2]

With marked inflammation, neutrophilic morphological changes are common in cats and are referred to as toxic changes. These are associated with neutrophilic cytoplasmic alterations including Döhle bodies, basophilia, vacuolization, and granulation.[1-3] Giant neutrophils (>13 µm) (Figure 61-1), observed most commonly in cats, also are considered a toxic change when associated with an inflammatory response during increased neutropoiesis; however, they also may be associated with myelodysplastic syndrome or myeloproliferative disease (feline leukemia virus [FeLV] associated).[4] Nuclear toxic changes do occur but are observed less frequently and are less reliable indicators.[1] Toxic changes occur during maturation and affect primarily myelocytic and metamyelocytic stages within the marrow, resulting from accelerated neutrophil production and release from marrow stores.[1] Döhle bodies are the most common toxic change observed and appear as minute, angular,

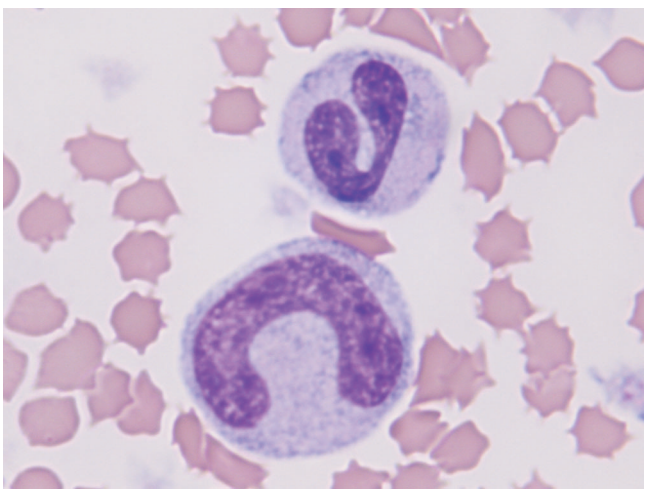

Figure 61-1. Two neutrophils are present: a mature segmenter and a giant band with diffuse cytoplasmic basophilia. Both the giant cell size of the band neutrophil and diffuse basophilia are characteristics of toxic change (Wright's stain).

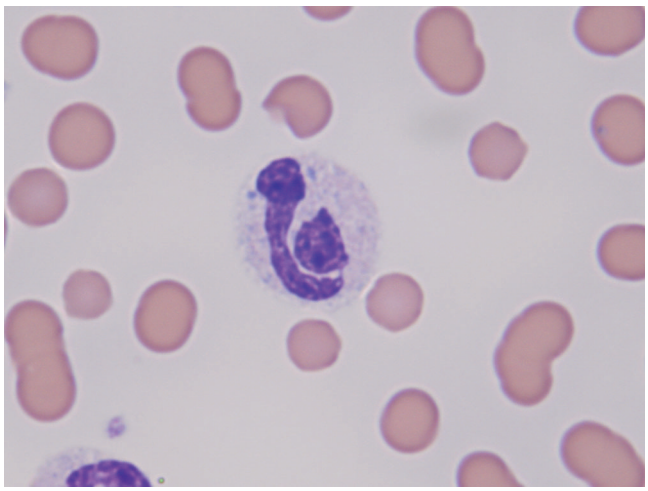

Figure 61-2. A mature segmented neutrophil with small angular bluish-gray cytoplasmic inclusions called Döhle bodies. These are small aggregates of endoplasmic reticulum and characteristics of mild toxic change (Wright's stain).

single to multiple, bluish-gray, retained aggregates of endoplasmic reticulum within the cytoplasm (Figure 61-2). Regardless of the number of Döhle bodies observed, these are indications only of mild toxic change[1,2] and occasionally may be present in a healthy leukogram.[1] Diffuse cytoplasmic basophilia occurs as a result of retention of polyribosomes within the cytoplasm (see Figure 61-1).[1,2] Vacuolization is associated with systemic toxemia from cytoplasmic granule dissolution[2] but also can occur artifactually (old blood specimens). Neutrophilic toxic granulation is uncommon to rare but, when present, indicates extreme toxicity and occurs when primary (azurophilic) granules within the cytoplasm retain granules containing mucopolysaccharides that stain red with Romanowsky's stains.[1,2] Toxic granulation must be differentiated from inherited mucopolysaccharidosis (see below) and Birman cat neutrophil granulation anomaly (see below).

Because neutrophils are the predominant leukocyte in peripheral blood, leukopenia most often is associated with neutropenia. Neutropenia (<2500/μL) occurs when tissue demand for neutrophils surpasses bone marrow replacement and counts fall below reference values. This is associated generally with increased loss or emigration, destruction, and/or deficient production or release.[1,2]

Deficient production of neutrophils often involves all cell lines within the bone marrow, but decreased neutrophils frequently are the first observed cell line to decrease on the leukogram. Stem cell death can be seen with FeLV, feline immunodeficiency virus (FIV), feline parvovirus (feline panleukopenia) infections, drug interactions, and/or myelophthisic disorders.[1]

Approximately 50 per cent of cats with FeLV-related illness present with a neutropenia and commonly leukopenia.[1,3] Three leukogram patterns have been described for FeLV-related diseases, including a mild neutropenia with normal hematopoiesis; moderate neutropenia with hypoplastic marrow; and severe persistent neutropenia with marrow granulocytic hyperplasia.[1,3] The leukogram pattern of the mild neutropenia with normal-appearing bone marrow is presented most commonly.[1,3] Moderately neutropenic cats that present with granulocytic hypoplasia of the bone marrow are referred to as having a panleukopenia-like syndrome. These cats, however, do not exhibit gastrointestinal signs as do those with panleukopenia virus.[1,3] The severe neutropenic form with granulocytic hyperplasia is referred to as hematopoietic dysplasia, preleukemia, or subleukemic granulocytic leukemia.[1,3] This form retards the maturation and release of neutrophils along with causing a viral-induced destruction of stem cells.[1] Bone marrow hyperplasia is present in the most severe form and must be differentiated from the early recovery phase of feline parvovirus.[3] Many times insufficient quantity of FeLV virus antigen is present within the peripheral blood to obtain a positive FeLV test and, if this occurs, a bone marrow immunofluorescent antibody (IFA) test for FeLV is recommended.

Another documented cause of neutropenia is a cyclic hemopoiesis syndrome, recognized primarily by cyclic neutropenia in FeLV-infected cats.[2,3] Neutrophil cycling occurs every 8 to 18 days and is characterized by neutropenia followed by a recovery to healthy cell counts.[3] Monocytosis may be a signal associated with a return of neutrophil numbers because no monocyte storage pool exists; therefore monocytes are released into circulation at an earlier age than neutrophils.[2]

Neutropenia also has been associated with FIV-positive cats and these cats are more susceptible to other infectious diseases.[3]

Feline parvovirus infection (panleukopenia) is seen infrequently but can be recognized by the presence of severe neutropenia (<1000/μL) with concurrent lymphopenia and a hypoplastic to hyperplastic bone marrow.[3] Because the virus affects all myeloid precursors, a bone marrow examination may show a near absence of myeloid series cells.[3] Given proper supportive treatment, recovery of neutrophil numbers occurs typically in approximately 5 days but occasionally may be remarkable, within 24 hours.[3] A neutrophilia (20,000 to 30,000/μL) with a left shift and toxic change is observed commonly during recovery.[3] Also, in contrast to other species, giant neutrophils or metamyelocytes may be present in circulation with recovery from severe neutropenia in cats.[1,3] During this recovery phase, bone marrow aspirates may have a radically different appearance with an abundance of early myeloid series cells and few mature segmented neutrophils.[2,3] As a result, this bone marrow pattern could be misinterpreted as evidence of a leukemic disorder,[3] and sequential interpretation of the leukogram is essential for accurate interpretation.

Administration of certain drugs, including chloramphenicol and chemotherapeutic drugs, can suppress bone marrow granulopoiesis inducing an idiosyncratic neutropenia.[2,3] Chloramphenicol is used infrequently, with toxicity observed after high-dose administration or chronic administration of low dosages.[3] Neutropenia associated with chemotherapeutic drugs often is expected, because these drugs attack rapidly dividing cells such as those present within hematopoietic tissue. Generally, drug-induced effects are reversible and neutropenia often resolves within 7 days after withdrawal of the offending drug[3] (see Chapter 69).

Neutropenia also may be caused by myelophthisic diseases resulting from replacement of normal hematopoietic tissue with neoplastic cells or connective tissue.[3] Myelophthisic diseases include leukemias, metastatic neoplasms, myelofibrosis, granulomatous diseases (i.e., disseminated histoplasmosis), and osteopetrosis.[1] Often, all hematopoietic cell lines are affected eventually, which results in circulating pancytopenia.[1,3] In these

cases, bone marrow aspirates and core biopsy specimens often are helpful for diagnostic purposes.[1,3]

Pathological redistribution or sequestration processes also may affect neutrophils and present with neutropenia. Early after initial exposure to gram-negative bacteria and/or endotoxins, neutrophils marginate rapidly, exit the CNP to merge with the MNP, potentiate aggregation of cells within small vessels, and cause a dramatic, occasionally transient pseudoneutropenia.[1] This may be followed by a true neutropenia resulting from neutrophil tissue emigration and eventually, with adequate bone marrow response, a neutrophilia.[1,3] Neutropenia sequestration may occur after blood transfusions or may be associated with hypersplenism.[1]

When a specific cause of neutropenia cannot be identified, this is described as idiopathic neutropenia. Immune-mediated causes have been considered for idiopathic neutropenia but positive results from specific laboratory tests have not been observed.

In some cats, neutropenia is observed with no overt clinical abnormalities. Even with exhaustive testing, abnormalities are not identified. These cats presumably are healthy even though they have "abnormally low" neutrophil values. Reference values are designed to detect 95 per cent of "healthy" animals. Therefore as many as 5 per cent of truly "healthy" cats may have values outside (higher or lower) well-prepared reference values. Reference values can be affected by such influences as age, breed, gender, nutrition, environment, geographical region, and testing equipment. These neutropenic cats may be similar to those "healthy" Belgian Tervurens with a neutropenic/leukopenic leukogram.[4]

Neutrophilia (>12,500/µL) commonly occurs because of a shift of MNP to the CNP, but other mechanisms include decreased egress of neutrophils from circulation, increased release from bone marrow storage pool, increased bone marrow production, or any combination of these. A physiologic or stress leukogram presents with a moderate neutrophilia as described previously and is associated with shifting of neutrophils between MNP and CNP.

During infection or inflammation, neutrophil counts between 15,000 and 30,000/µL are most common, with marked neutrophilia occurring with numbers above 30,000/µL.[2] Often, these counts are associated with a localized or generalized bacterial, viral, fungal, or parasitic infection. Localized infections such as pyometra, pyothorax, abscesses, or peritonitis often show the most pronounced neutrophilias and commonly demonstrate a left shift with toxic changes.[3] The degree of neutrophilia is dependent on the ability of the bone marrow to produce and release cells, and the severity and duration of the disease process. Often, after surgical resolution, as with a hysterectomy for a pyometra, the magnitude of the neutrophilia actually increases transiently because of the continued stimulation and proliferation of the bone marrow pool and decreased tissue utilization of neutrophils. In this case, bone marrow aspirates show marked granulocytic hyperplasia; therefore, myeloid series cell proliferation does not just shut down after removal of the offending tissue like a light switch but decreases gradually when stimulatory factors are diminished abruptly. When extreme neutrophil counts (>50,000/µL) associated with a marked left shift containing myelocytes, promyelocytes, and myeloblasts are present, this is called a "leukemoid response" and may be difficult to differentiate from acute granulocytic leukemia.[1,2] A bone marrow aspirate may help differentiate acute granulocytic leukemia from a leukemoid response but must be interpreted with care.

Generalized or systemic disease resulting from infection with fungi, bacteria, viruses, or parasites may produce a variable neutrophil response.[3] Often a mild to moderate neutrophilia is observed with feline infectious peritonitis or feline herpesvirus-1 infection.[3] Feline infectious peritonitis and toxoplasmosis may present with either an increase or decrease in neutrophil numbers, with toxoplasmosis more likely causing a neutropenia.[3]

Other causes of neutrophilia are associated with inflammatory conditions or trauma without infectious organisms. These disorders usually cause a mild to moderate neutrophilia and include surgery, immune-mediated diseases, hemolysis, sterile foreign body, burns, soft tissue trauma, uremia, tissue necrosis, hemorrhage, and/or neoplasms (secondary tissue necrosis).[2,3] Predictably, the magnitude of the neutrophilia and presence of a left shift are dependent on the longevity and severity of the inflammatory condition.[1,2]

LYMPHOCYTES

Lymphocytosis is especially common in cats, identified when lymphocyte counts increase above reference values (>7,000/µL).[1] The clinician must be cautious when viewing feline blood smears under light microscopy because differentiating small lymphocytes from nucleated erythrocytes can be extremely difficult to the untrained observer (Figure 61-3). Young cats usually have higher lymphocyte counts than adult cats.[1] Lymphocytosis in young cats, less than 1 year old, most often is associated with a physiological response to epinephrine release (physiologic leukocytosis), but because lymphocytic diseases are common, the cause of any occurrence of persistent lymphocytosis must be identified.[1] Antigenic stimulation can cause lymphocytosis and produce reactive lymphocytes, also referred to as immunocytes, which are observed in peripheral blood smears. Reactive lymphocytes are larger than

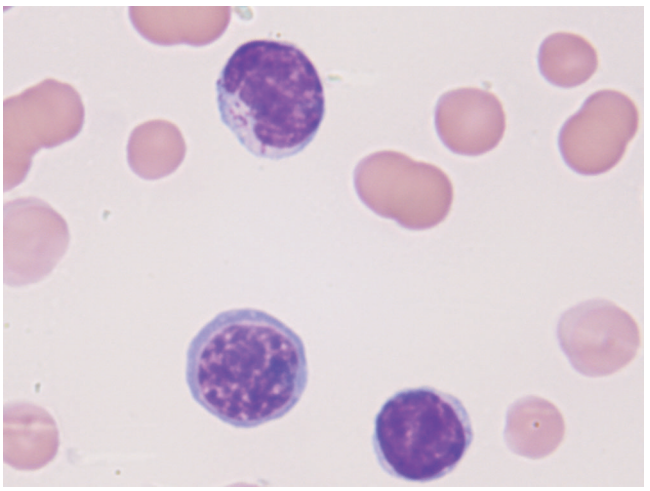

Figure 61-3. Two small lymphocytes and a nucleated erythrocyte (rubricyte stage). One lymphocyte contains a few magenta cytoplasmic granules *(upper),* and the other is a normal small lymphocyte *(lower right).* The rubricyte *(lower left)* has deeper blue cytoplasm with more coarsely clumped nuclear chromatin. Nucleated erythrocytes can be difficult to differentiate from normal small lymphocytes (Wright's stain).

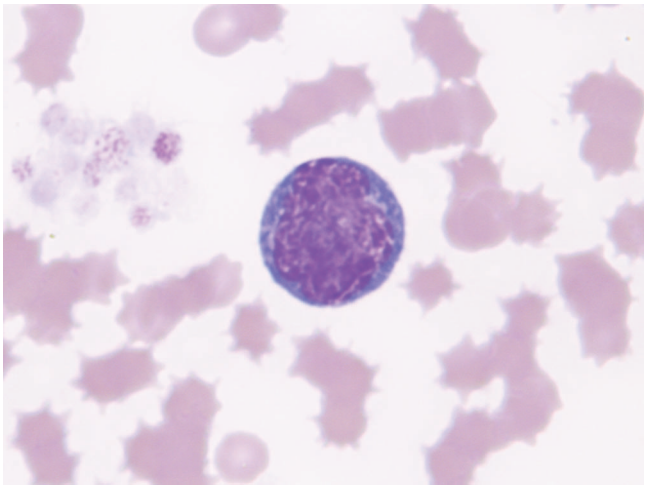

Figure 61-4. Reactive lymphocytes (immunocytes) are larger than normal small lymphocytes, and distinguished by their deep blue cytoplasm and often irregularly shaped nucleus. When present, they are suggestive of recent antigenic activity such as vaccination (Wright's stain).

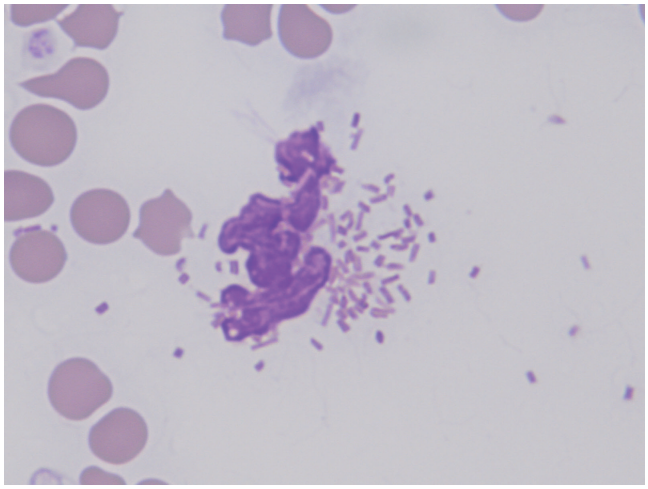

Figure 61-5. A ruptured eosinophil illustrating the characteristic rod-shaped, reddish-orange granules that distinguish this cell in cats. An intact eosinophil is present in Figure 61-6 (Wright's stain).

normal small lymphocytes and consist of a round to indented to irregularly shaped nucleus and deep blue abundant cytoplasm, occasionally containing one to a few clear round punctate microvacuoles (Figure 61-4).[3] This appearance helps differentiate reactive lymphocytes from immature lymphocytes (lymphoblasts), which usually are larger with a round, occasionally irregularly shaped nucleus with dispersed chromatin, and one or more prominent nucleoli.[3] Recent vaccination can elicit an antigenic response with reactive lymphocytes observed in peripheral blood.[1] Granular lymphocytes also may be observed normally within peripheral blood smears. These lymphocytes are natural killer (NK) cells and contain a few minute, magenta, perinuclear granules within the cytoplasm.

Lymphopenia is present when absolute numbers of lymphocytes are below reference values (<1,500/µL) and is observed commonly in ill animals.[2] Causes of lymphopenia include decreased production, increased destruction, increased loss, sequestration, or redistribution. Lymphopenia associated with a stress leukogram is observed most frequently.[2] If eosinophils in moderate numbers (>300/µL) are present, corticosteroid-associated lymphopenia is unlikely.[3] Other causes of lymphopenia are then considered, unless a cause for a concomitant eosinophilia is present. Decreased lymphocyte production is associated with rare hereditary immunodeficiency disorders, and increased loss is associated with viral diseases (feline panleukopenia, FeLV, and FIV), septicemia, endotoxemia, lymphocyte-rich thoracic effusions (chylothorax) (see Chapter 40), immunosuppressive therapy, radiation therapy, and gastrointestinal diseases (intestinal lymphangiectasia).[1,2]

MONOCYTES

Monocytosis (>850/µL) is a nonspecific finding in cats with little diagnostic application. However, monocytosis is associated with numerous acute and chronic conditions, including purulent inflammation, tissue destruction, neutrophilia, trauma, necrosis, malignancy, immune-mediated injury, hemorrhage, hemolysis, and pyogranulomatous inflammation.[1,2] Also, monocytes do not have a storage pool in the bone marrow and therefore are released earlier into peripheral blood during the maturation process, which often indicates a recovery from neutropenia.[2] In cats, monocytosis is not characteristic of the stress leukogram as it is in dogs.[1,2]

Monocytopenia is of little significance and this finding is clinically unimportant.[1,2]

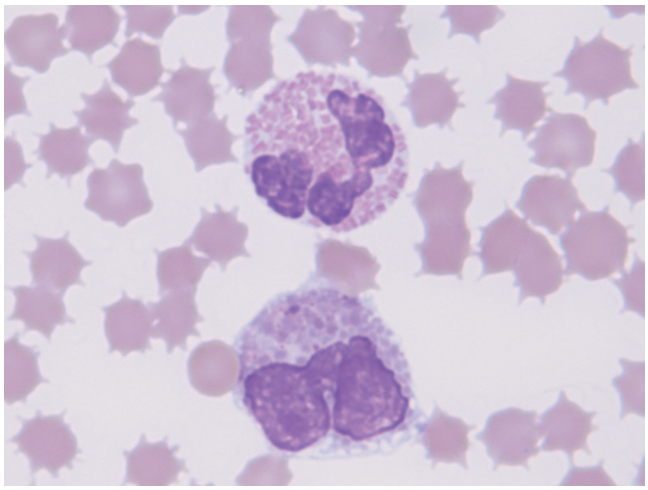

Figure 61-6. The upper cell in this photomicrograph is a normal eosinophil with rod-shaped, reddish-orange granules. The lower cell is a normal feline basophil with lavender round to rod-shaped granules (Wright's stain).

EOSINOPHILS

Feline eosinophils are identified easily via light microscopy as a result of their morphologically unique red-orange, rod-shaped granules (Figures 61-5 and 61-6). Eosinophilia (>750/µL) is a relatively common finding and identified when the absolute eosinophil count is increased above reference values. Increased eosinophils occur because of increased production and/or release of eosinophils from bone marrow reserves. Upper limits may vary depending on the laboratory used. Eosinophils

normally are present in low numbers; therefore, reference interval determination is complex and interpretation must be done with this in mind (see section on laboratory data information).

Disorders associated with eosinophilia are numerous, and the clinician should not assume automatically that it is associated with parasitism (see Chapter 26). Parasitic conditions associated frequently with eosinophilia include ectoparasitism, such as fleas or ticks; and endoparasitism, with eosinophilia most often the result of active migration of parasites with subsequent tissue injury, as in aelurostrongylosis, paragonimiasis, toxocariasis, and dirofilariasis. Other disease processes causing an eosinophilia include immediate or delayed hypersensitivity (eosinophilic granuloma complex, asthma, eosinophilic keratitis, dermatitis, gastroenteritis, pneumonitis), neoplasm (eosinophilic leukemia, mast cell tumor, lymphoma, some carcinomas, fibrosarcoma, and thymoma), infectious organisms (*Cryptococcus*, some strains of FeLV, pythiosis, and some bacteria—staphylococcal and streptococcal infections), hypereosinophilic syndrome (HES), and hyperthyroidism.[1-3]

The degree of eosinophilia does not specify one disease over another; however, flea-bite allergic dermatitis and eosinophilic granuloma complex cause the highest eosinophil counts most frequently.[3,5] HES is a rare disorder often associated with very high eosinophil counts.[3,5] Therefore interpretation of eosinophilia likely requires extended testing beyond the minimum database. Besides the CBC, the remainder of the full database, including serum chemistry profile, urinalysis, and fecal flotation, is warranted. Other tests to consider include, but are not limited to, thoracic and abdominal radiographs, bone marrow aspirate, heartworm antigen and antibody testing (see Chapter 36), FeLV test, FIV test, toxoplasma titers, intestinal endoscopy and biopsy, microbiological cultures, fine-needle aspirates of masses or enlarged organs, total serum thyroxine (T_4), tracheal wash/bronchiolar alveolar lavage (BAL), ultrasonography, and tissue biopsies. All ancillary testing would be subject to repeated physical examinations, historical information, geographic location, travel history, present environment, nutrition, and negative testing on original database.

Eosinopenia is associated most commonly with a stress leukogram (endogenous or exogenous corticosteroids), but true significance is difficult to interpret clinically.[1-3]

BASOPHILS

Basophils normally are the least common leukocyte observed in normal feline peripheral blood smears.[3] They are slightly larger than neutrophils, with unique microscopic morphology consisting of a lobed, ribbon-shaped nucleus with round to slightly rod-shaped granules expanding the cytoplasm. Granules may be difficult to recognize and often are overlooked by the untrained observer.[2,3] Focusing the microscope up and down on oil power (100×) often makes identification of granules easier. With Romanowsky staining, these granules are lavender-gray in color, rather than the deep purple (metachromatic) staining of other species (see Figure 61-6).[2,3] Occasionally, feline basophils have one or more deep purple (metachromatic) to black staining granules with early release from marrow stores. Because of the slight cytoplasmic color differences between basophils and neutrophils, basophils may be classified incorrectly as neutrophils with toxic change.

Although basophilia (>200/µL) is observed uncommonly, when present, it is associated frequently with a concomitant peripheral eosinophilia.[1-3] Conditions associated with a basophilia include dirofilariasis, eosinophilic granuloma complex, polycythemia vera, basophilic leukemia, myeloid leukemia, and hypersensitivity reactions.[1-3] Interpretation of basophilia would be similar to eosinophilia, because of the usual association of a concomitant eosinophilia with basophilia. Counting only three basophils on a blood smear 100-count differential with a 10,000/µL total leukocyte count puts numbers above upper reference values and care should be taken with interpretation.

Basopenia is not recognized as a clinical problem.[1,3]

LEUKOCYTE DISORDERS

Pelger-Huët Anomaly

Pelger-Huët (P-H) anomaly is a benign congenital disorder of leukocyte development reported in eight domestic short-haired cats.[6] It is thought to be transmitted as an autosomal dominant trait; however, incomplete penetrance has been observed in Australian shepherds.[6,7] The heterozygous form is present; the homozygous form appears to be lethal in utero. The homozygous phenotype is characterized by skeletal abnormalities in rabbits; however, rare homozygous human beings have survived into their nineties.[6]

The distinguishing cytological characteristic of P-H is hyposegmentation of nuclei within granulocytes and monocytes in the presence of a fully mature, coarsely clumped chromatin pattern (Figure 61-7).[6] Nuclear morphology often is variable and may be round, oval, dumbbell-shaped, peanut-shaped, band, or even bilobate.[6] The bilobate shape consists of two nuclear lobes connected by a fine filament often referred to as "pince-nez" or eyeglass-shaped nucleus.[6] Careful attention to granulocyte morphology and the presence of hyposegmented nuclei in eosinophils (Figure 61-8) and other cell lines may give indications of this anomaly. Female Barr bodies are absent or extremely rare in P-H.[6]

Biochemical assays including nitroblue tetrazolium (NBT) dye reduction, hexose monophosphate shunt activity, superoxide generation, chemiluminescence, protein iodination, phagocytosis, and bactericidal activity are normal in P-H dogs.[6]

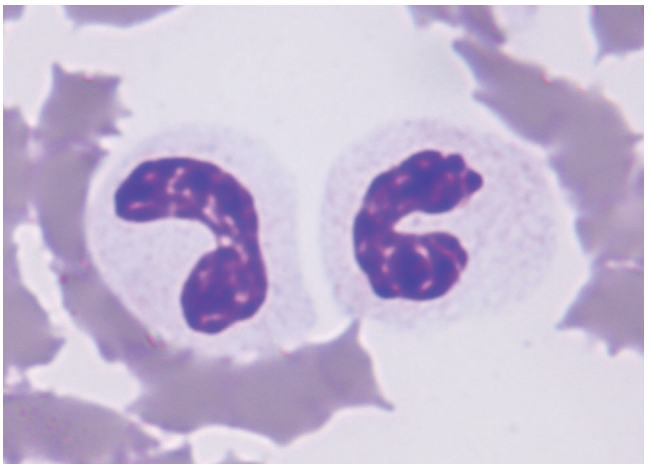

Figure 61-7. Two neutrophils in a cat with heterozygous Pelger-Huët anomaly showing hyposegmented nuclei (band-shaped) containing well-clumped, coarse, mature chromatin (Wright's stain).

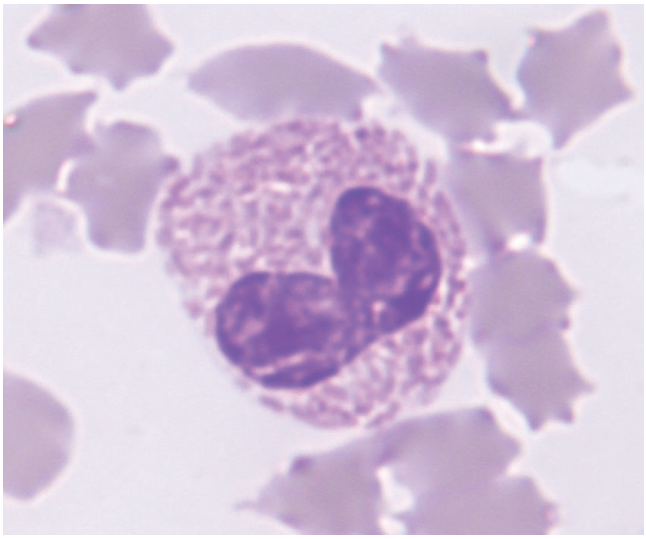

Figure 61-8. Eosinophil of a cat with heterozygous Pelger-Huët anomaly showing a hyposegmented nucleus, whose shape appears similar to an immature (metamyelocyte stage) eosinophil, containing well-clumped coarse mature chromatin and characteristic rod-shaped granules (Wright's stain).

Hematological manifestations of P-H often are reported as a persistent degenerative left shift without toxic changes. These findings are unexpected on a routine CBC from a clinically healthy animal.[6] Earlier precursors such as myelocytes, metamyelocytes, and bands may be reported; however, the chromatin of these cells is fully matured (well clumped).[6] This anomaly must be recognized to avoid unnecessary, expensive, and potentially invasive laboratory tests and treatments. A veterinary clinical pathologist can assist in diagnosis of P-H.

P-H anomaly must be differentiated from pseudo–P-H anomaly, which often is a transient acquired condition that resolves with proper diagnosis and treatment.[6] Pseudo–P-H has been associated with a number of diseases and drug administration, including various forms of leukemia and preleukemic conditions, antineoplastic drugs, and ibuprofen.[6] Drug-associated changes are idiosyncratic and resolve after treatment withdrawal.

Treatment of this anomaly is not necessary because neutrophil function is not compromised.

Chédiak-Higashi Syndrome

Chédiak-Higashi syndrome (CHS) is a rare inherited autosomal recessive trait found in smoke blue Persian cats.[8,9] This disease typically is characterized by partial oculocutaneous albinism, photophobia, neurological abnormalities, bleeding abnormalities, and recurrent infections, generally resulting in death at an early age.[8] Some researchers have not observed an increased tendency toward infections in CHS cats, but neonatal kittens from a colony of CHS cats were markedly more susceptible to infections (bacterial, viral) and acute death from hemorrhage that contributed to a lower-than-average survival time when compared with healthy cats.[10] Susceptibility to bacterial infections is associated with multiple defects within the defense system. Neutropenia occurs as a result of impaired bone marrow release of mature neutrophils. Defective intracellular killing of phagocytosed bacteria also is present.[8]

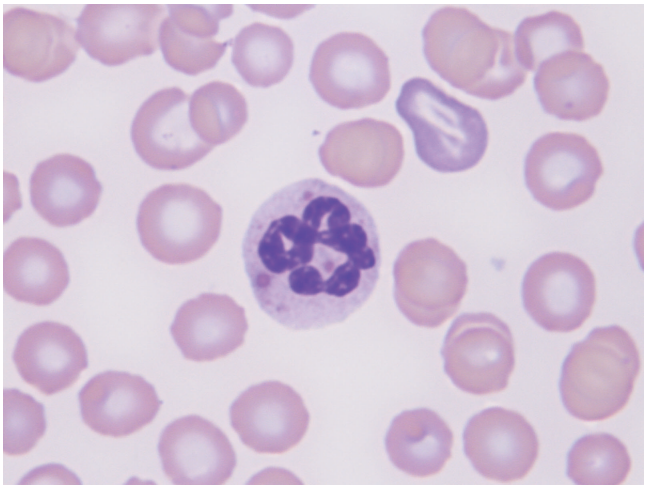

Figure 61-9. Neutrophil from a Chédiak-Higashi fox. Note the scattered, light red, variably sized cytoplasmic lysosomal inclusions characteristic of this syndrome within the cytoplasm (Wright's stain).

Affected Persian cats with hereditary genes for CHS have a coat color termed "blue smoke," which is a lighter color than the traditional "blue smoke" of Persian cats without CHS.[9] Ocular abnormalities also are present such as photophobia, lighter irises (light green, light yellow, or light yellow-green). Many affected cats also have congenital cataracts, a red fundic light reflection compared with a yellowish-green reflection from normal Persian cat fundi, and less fundic pigmentation.[9] Tapetal regions may not be apparent and the underlying choroidal vasculature is only partially visible.[9] Tapetal defects are associated with tapetal rod degeneration within tapetal cells in kittens ages 2 weeks to 4 weeks.[8]

The gene abnormality associated with CHS has not been identified in cats but has been defined as the homologous *beige* gene in mice and human beings, which is a 5-kilobase pair deletion.[8] The function of this gene is unknown.[8] CHS was hypothesized to be caused by microtubular-forming abnormalities, but this has been disproven.[8]

Hematologically, neutrophils, eosinophils, and basophils contain enlarged, lightly eosinophilic cytoplasmic granules observed with Wright's staining (Romanowsky's stain) (Figure 61-9).[8] Occasionally, monocytes and lymphocytes may contain a single eosinophilic cytoplasmic granule.[8] Histologically, melanocytes contain enlarged melanin granules in hair shafts, and renal tubular epithelial cells contain enlarged granules.

Prolonged bleeding times (three times normal), manifested as hematomas after surgical procedures, are the result of a platelet storage pool defect (SPD). Impaired platelet aggregation associated with virtual absence of adenine diphosphate and serotonin (dense granules) may account for the abnormal aggregation.[8] Platelet counts and coagulation times (prothrombin time [PT] and partial thromboplastin time [PTT]) are within reference intervals[9] (see Chapter 60).

Presumptive diagnosis can be made by observation of a Persian cat with light "blue smoke" color, lightly colored irises, red fundic reflection, depigmented fundic area, and bleeding tendencies.[9] Also, hair shaft examination can be performed by extracting hair from a suspected CHS cat and a normal cat, placing the hair shafts on a microscopic slide, adding immersion oil, then gently pressing a coverslip over the hair shafts.[9]

Examination under low or high dry power reveals enlarged, clumped melanin granules in CHS when compared with a normal hair shaft.[9]

With Romanowsky staining, CHS cytoplasmic granules within neutrophils appear as light eosinophilic inclusions that must be differentiated from Döhle bodies associated with neutrophil toxicity.[9] If a question occurs about granule composition, differentiation can be made using peroxidase staining (CHS granules stain black).[9]

Cats with CHS do not require continuing treatment; however, great care should be taken to control hemorrhage resulting from the platelet SPD and prolonged bleeding times. Platelet transfusions can correct bleeding time temporarily if surgical procedures are to be performed.[8] Long-term correction of neutrophil and platelet function in CHS is possible only through bone marrow transplantation (BMT).[8] BMT has been performed in cats with correction of the neutrophil and platelet defects but no observable effect on lysosomal distribution within liver or kidney cells.[8] Neutrophil function is improved temporarily after treatment with recombinant canine granulocyte-colony stimulating factor (rcG-CSF) or interleukin-2 (IL-2) in cats.[8]

The "blue smoke" coat color is beautiful in Persian cats with CHS, but this is an undesirable trait to propagate. Breeders should be counseled against using affected cats or carrier cats, which are normal phenotypically. Because this is an autosomal recessive trait, both the sire and dam that produce offspring affected with CHS are obligate carriers and should be removed from the breeding stock. Administering drugs that affect platelet function, such as cyclooxygenase inhibitors, is contraindicated.[8]

Birman Cat Neutrophil Granulation Anomaly

Neutrophil granulation anomaly is a hereditary trait characterized by increased granularity of neutrophils transmitted as an autosomal-recessive manner in purebred Birman cats.[11,12] The cytoplasm of affected neutrophils contains numerous fine, normal-size deep pink to purple granules, appearing similar to azurophilic granules found in promyelocytes. Normally, azurophilic granules become indistinct with Romanowsky stain in the myelocyte stage of development but seem to persist throughout the maturing process in this anomaly.[11] Lymphocytes, eosinophils, monocytes, and basophils appear morphologically normal.[11] The abnormality was concluded to be due to an alteration within the contents of cytoplasmic granules with increased affinity for acid dyes.[11] Neutrophil function is not compromised.[11] Bactericidal activity was not different from unaffected neutrophils; therefore, treatment is not necessary. The main concern is to differentiate this anomaly from mucopolysaccharidosis (MPS VI and VII) and toxic granulation.[12]

Hypereosinophilic Syndrome

Hypereosinophilic syndrome (HES) is a disease of unknown origin occurring with characteristics of persistent peripheral eosinophilia and organ infiltration by eosinophils eventually causing organ failure and death[13,14] (see Chapter 26). Peripheral eosinophil counts in HES of 3,500/µL to 130,000/µL have been observed. Occasionally, mild anemia also is present. Bone marrow, spleen, liver, mesenteric lymph nodes, and gastrointestinal tract were the organs infiltrated most frequently; however, any organ(s) may be affected.[13,14] Difficulty occurs in differentiating HES from eosinophilic leukemia (EL), which may be impossible because both conditions may be a variant of the same disease.[13] EL often contains more immature eosinophils within the peripheral blood, it causes a more severe anemia, and the M:E ratio in bone marrow is greater than 10:1.[13,14] One report observed a predisposition in female cats (male to female ratio of 4:11).[13]

Clinical signs are relatively nonspecific, varying with the organ(s) affected, and include diarrhea, weight loss, anorexia, pyrexia, and pruritus.[13,14] Longevity is difficult to establish; however, some cats have exhibited clinical signs related to HES for 3.5 years.[14]

HES is a progressively fatal disease with no effective treatment; however, Gleevec (Imatinib mesylate; formerly STI571, a signal transduction inhibitor) has been used in human beings with excellent results. Corticosteroids, hydroxyurea, and α-interferon also have been used in human beings with variable results and when effective, unwanted side effects are common.

Lysosomal Storage Diseases

Many lysosomal storage diseases (LSDs) have been identified in cats; however, all are rare and only a few present with microscopic abnormalities within peripheral blood leukocytes. Only observable leukocyte morphological changes are discussed. Specific leukocyte activity has not been tested, but microscopic characteristics may be a simple method to help identify and/or classify many storage diseases.

Hematological alterations of leukocytes in cats are associated with sphingomyelinosis (Niemann-Pick disease); α-mannosidosis; mucopolysaccharidosis (MPS) I, VI, and VII; GM_1 gangliosidosis; and GM_2 gangliosidosis.

Leukocytes in MPS I, VI, and VII must be differentiated from toxic changes within neutrophils and Birman cat neutrophil granulation anomaly.

Sphingomyelinosis has been reported in Siamese, Balinese, and domestic short-hair cats. Disease is caused by a deficiency of sphingomyelinase resulting in accumulations of sphingomyelin, cholesterol, and gangliosides within the brain, liver, spleen, and bone marrow. Large vacuolated macrophages may be observed within the peripheral blood.

α-Mannosidosis, reported in Persian, domestic short-hair, and domestic long-hair cats, is due to a deficiency of α-mannosidase that leads to an accumulation of mannose oligosaccharides within the central nervous system, skeleton, and spleen. Lymphocytes, granulocytes, and monocytes within peripheral blood appear vacuolated.[15]

MPS I occurs in domestic short-hair cats. This LSD is caused by a deficiency of α-L-iduronidase. Some observers have reported small pink granules within neutrophil cytoplasm.[15]

MPS VI is reported in Siamese cats and is caused by a deficiency of arylsulfatase (Figure 61-10). Peripheral neutrophils, lymphocytes, basophils, eosinophils, and monocytes are affected. The cytoplasm of neutrophils often appeared foamy and contained uniform small metachromatic granules, often located within a vacuole.[16] Lymphocytes have been divided into three distinct types: normal appearing, some containing vacuoles with small dark metachromatic granules, and a few containing empty vacuoles.[16] Nearly all monocytes contained vacuoles, and a moderate percentage contained dark granules

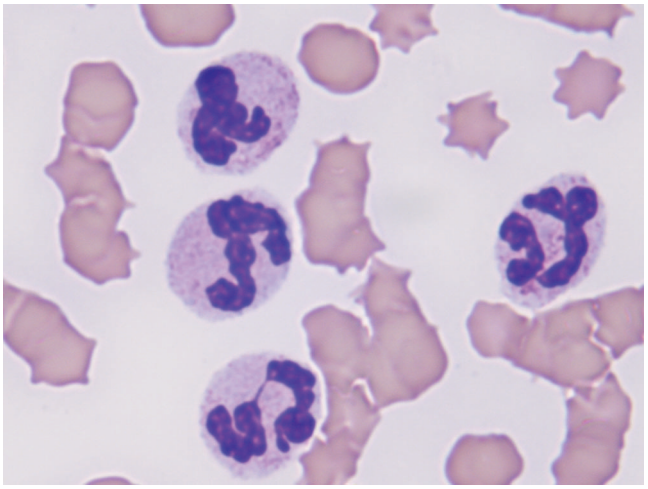

Figure 61-10. Note the cytoplasmic color change present in a cat associated with MPS VI (Wright's stain). The granularity is similar to and must be differentiated from toxic granulation and Birman cat neutrophil granulation anomaly.

within these vacuoles.[16] Eosinophils contained cytoplasmic vacuoles, and basophils contained large reddish-purple cytoplasmic inclusions or granules.[16] Basophils had the largest granules.[16]

MPS VII, reported in domestic short-hair cats, is caused by a deficiency of β-glucuronidase. Neutrophils and lymphocytes contain deep purple cytoplasmic inclusions that should not be confused with toxic changes. Granules stain purple with toluidine blue dye.[16]

GM_1 gangliosidosis has been reported in domestic short-hair, Korat, and Siamese cats. It is caused by a deficiency in β-galactosidase. Lymphocytes contain small, distinct, clear cytoplasmic vacuoles.[15]

GM_2 gangliosidosis, reported in domestic short-hair and Korat cats, is caused by a deficiency of β-hexosaminidase. Neutrophils contain dark blue granules, and lymphocytes contain prominent azurophilic cytoplasmic granules.[15]

CONCLUSION

Interpretation of the leukogram can be a straightforward assessment or can follow a convoluted path. When interpreting the feline leukogram, the clinician encounters many differences from other species, including cell responses and cell morphology. Although much information may be gained from an initial leukogram, multiple CBCs often are necessary to observe changes, trends, or evidence of disease. Well-prepared blood smears can be sent to a veterinary clinical pathologist for evaluation if an abnormal or unusual morphology is observed. Changes in the leukogram may occur rapidly, and interpretation is seen as an evolving spectrum of adjustments revolving around collating and assessing all aspects of diagnostic evaluations including signalment, history, physical examination, and drug treatment with potential frequent monitoring of laboratory parameters. Knowledge of how reference values are determined also helps the clinician with assessing a leukogram while helping to avoid overinterpretation. All aspects of interpretation are necessary to assess and identify subtle changes accurately that are associated with disease/anomaly detection.

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Chapter 62

Plasma Cell Neoplasms

Leslie E. Fox

Plasma cell tumors are a group of diseases characterized by malignant proliferation of plasma cells that have differentiated from B lymphocytes. They are rare in cats and can be difficult to diagnose definitively. Plasma cell tumors are believed to be derived from a single B cell programmed to make a specific type of immunoglobulin (IgA, IgG, IgM, IgE, IgD) or segment of immunoglobulin protein (light chains and other fragments). Multiple myeloma (MM) traditionally has been described as a collection of clinicopathological findings caused by malignant plasma cells that originate typically in bone marrow. Minimal criteria for diagnosis of MM include bone marrow plasmacytosis with greater than 20 per cent plasma cells and one of the following abnormalities: monoclonal protein in the serum, Bence-Jones proteinuria (monoclonal protein in the urine), or lytic bone lesions.[1] Monoclonal proteins produced by malignant plasma cells also are called myeloma proteins, M proteins, M-component, or paraproteins.

Clinical presentations in cats in order of decreasing frequency include MM, solitary plasmacytomas originating in soft tissues (solitary extramedullary plasmacytomas) or in a focal area of bone marrow (solitary osseous plasmacytomas), and a syndrome of excessive IgM production called Waldenstrom's macroglobulinemia.[2] Inappropriately high immunoglobulin protein concentration causing hyperviscosity syndrome is responsible for a spectrum of paraneoplastic disorders for which the cat may be presented, affecting the kidneys, eyes, neurological function, coagulation system, and heart.[3]

ETIOLOGY

The cause of plasma cell tumors in cats is undetermined. Retroviral infection (feline leukemia virus [FeLV], feline immunodeficiency virus [FIV]) is not associated with MM.[4] Environmental factors, such as exposure to ionizing radiation (radiologists in addition to patients that receive multiple diagnostic radiographs), therapeutic mineral oil exposure, silicon, some metals, agricultural chemicals, and petroleum and benzene-derived chemicals, have been associated with an increased risk of MM in human beings and may play a role in etiopathogenesis in companion animals.[1] Genetic factors and chronic inflammation/infection also play a role.

EPIDEMIOLOGY

The incidence of plasma cell tumors in cats is undetermined but appears low.[2] Two collections of cases together describe features of MM in 61 cats. Information abstracted from case reports and retrospective analyses of 33 cats diagnosed before 2001 was summarized by Ogilvie and Moore.[4] A Veterinary Cooperative Oncology Group (VCOG) retrospective study described 29 additional cats.[5] Most cats with MM were middle-age to elderly domestic shorthairs, typically older than 3 years.[4,5] No gender predilection was evident. Extramedullary soft tissue plasmacytomas are found in middle-age shorthair cats with an apparent male gender predilection.

CLINICAL PRESENTATIONS

Multiple Myeloma

Nonspecific clinical signs such as depressed activity, lethargy, weakness, inappetence, and weight loss are common findings reported for almost all cats with MM.[4,6] In the VCOG study, clinical signs identified frequently also included cardiac murmur, peripheral lymphadenomegaly, ascites, and generalized pain.[5] Typically, clinical signs have been present for 4 to 7 weeks before presentation; however, a few cats displayed clinical signs for more than 1 year.[4,5] Other nonspecific signs may include intermittent vomiting and diarrhea.[4,5]

Although vague initial clinical findings are common to cats, dogs, and human beings with MM, important species differences exist. In dogs and human beings, signs referable to bone involvement are most common.[1,6] Soft tissue dissemination of malignant plasma cells resulting in enlarged abdominal organs is a feature found commonly on initial physical examination in most reported feline cases.[4,5] Hepatomegaly and/or splenomegaly caused by plasma cell infiltration was common to more than 70 per cent of cats with concurrent bone marrow involvement in the VCOG study.[5] Renomegaly and abdominal lymphadenomegaly also may be detected.[4,5] In human beings, soft tissue dissemination is considered a terminal event.[7]

Bone lysis is not a prominent feature of MM in cats when compared with dogs and human beings.[4,5] Generalized pain was frequent in the VCOG study, which may be referable to a local effect of malignant bone marrow plasmacytosis even without

significant osseous invasion.[5] If cats do have bony plasma cell infiltration causing bone lysis, then localizable pain and associated lameness could be attributed to focal lytic lesions.[4] Spinal cord compression, resulting in pain, hind limb paresis, and ataxia, has been reported secondary to a lytic vertebral body lesion.[8] Pathological fractures are rare.[4,5,8]

MM-associated paraneoplastic disorders are not reported as frequently in cats as in affected human beings or dogs.[4,5] Clinical signs caused indirectly by MM most commonly are a result of serum hyperviscosity, which slows blood flow and affects almost every body system.[3] Consequences of serum hyperviscosity are variable and cannot be predicted easily from serum globulin type or concentration.[1] Evidence of renal insufficiency may include polyuria/polydipsia, dehydration, and inappetence and may be the only presenting complaints.[4] Bleeding diatheses consisting of epistaxis, gingival bleeding, melena, and pleural and peritoneal hemorrhagic effusions have been observed.[4] Ophthalmic complications associated with hyperviscosity in cats include retinal hemorrhage with subsequent detachment and blindness, optic disc swelling, engorged retinal blood vessels, and intraretinal cysts[4] (Figure 62-1). Cardiovascular effects of hyperviscosity include cardiac murmur, tachycardia, bradycardia, gallop rhythm, and signs of congestive heart failure secondary to ventricular hypertrophy and increased cardiac effort.[4] Cats with MM may exhibit only neurological abnormalities such as seizures, behavior changes, and circling.[4] Localized infections (skin, kidney), sepsis, and fever are observed secondary to immunosuppression and may cause more morbidity than the plasma cell neoplasm.[4]

Occasionally, clinical signs result from the biological properties of the secreted M protein. Cryoglobulins are proteins that precipitate when serum is cooled to temperatures less than that of the normal body and dissolve when reheated. In one case reported in the literature, the cat presented with erythema, hemorrhage, and necrosis of the ears and extremities. This cat was febrile and lethargic. A monoclonal cryoglobulin IgG was identified and was thought to be the cause of the cold agglutinin signs. MM was diagnosed subsequently by finding significant plasmacytosis on bone marrow aspiration cytology.[9]

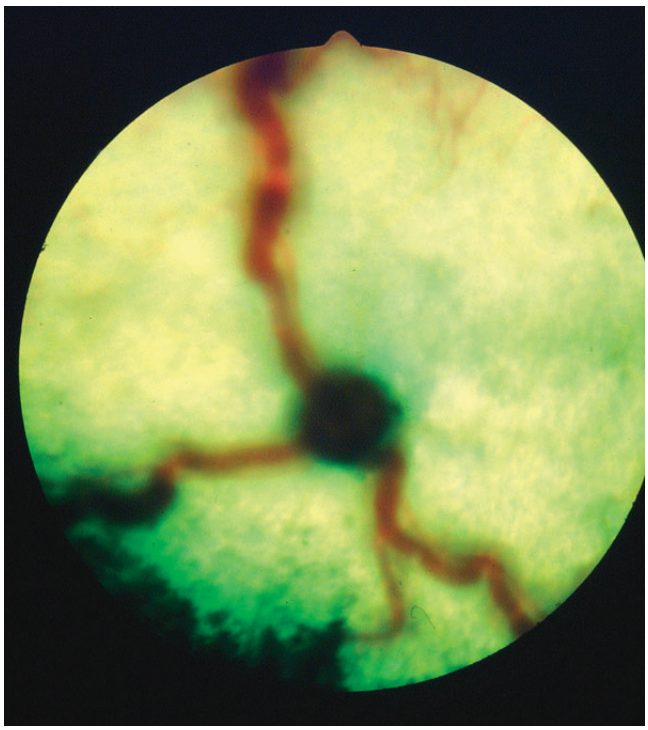

Figure 62-1. Fundus of cat with a monoclonal gammopathy. The retinal blood vessels appear dilated and demonstrate a characteristic "box-car" appearance due to intravascular sludging of blood. (Photo courtesy S. Pizzirani.)

Solitary Soft Tissue Plasmacytomas

Solitary extramedullary soft tissue plasmacytomas have been reported in cats and originate most commonly in the skin.[10] Other sites include the intestinal tract, liver, retroperitoneal space, globe (intraocular), periorbital muscle, oral cavity, mucocutaneous junction, and brain.[4,5] Clinical presentations reflect the location of the tumor. For example, a brain plasmacytoma was reported recently in a cat with abnormal neurological findings of compulsive circling to the left and a menace deficit in the right eye consistent with a focal prosencephalic intraparenchymal lesion.[11] Extramedullary soft tissue plasmacytomas typically are associated with paraprotein secretion and intratumor amyloid.[10,12,13] Metastasis to regional lymph nodes and organs is not uncommon. Disseminated soft tissue involvement with hyperglobulinemia is a frequent feature of MM in cats and is associated with a short survival time. Therefore a complete evaluation is needed to ensure that the extramedullary plasmacytoma has not disseminated. Although case numbers are small, solitary extramedullary plasma cell tumors involving skin or other soft tissues are aggressive and metastasize. The recent report of the progression of a solitary, cutaneous plasma cell tumor to MM demonstrates the need for a thorough initial diagnostic evaluation and periodic evaluation for disseminated disease.[14]

Solitary Osseous Plasmacytomas

Most cats with MM have soft tissue (typically visceral) involvement.[4,5] Few reports exist of cats with solitary osteolytic lesions at presentation. Solitary bone lesions have been found in the vertebral column, mandible, and maxilla. Unfortunately, cats with solitary bone lesions at first presentation eventually progress systemically to other bones and soft tissue.

DIFFERENTIAL DIAGNOSIS

Treatment and prognosis depend on the ability to distinguish reactive plasmacytosis from solitary or multifocal malignant plasma cell accumulations. Hyperglobulinemia is found in most cats with MM and in most patients with extramedullary plasmacytomas. Unfortunately, the presence of hyperglobulinemia or a monoclonal gammopathy is not diagnostic of neoplasia. Differential diagnoses for a monoclonal gammopathy are MM, lymphoproliferative diseases (systemic and cutaneous lymphoma), feline infectious peritonitis (FIP; typically polyclonal), chronic antigenic stimulation (lymphoplasmacytic gingivitis), and possibly infection with *Ehrlichia* spp. The frequency of plasma cell tumors associated with paraproteinemias is much greater than with other B-cell tumors, such as lymphoma.

DIAGNOSIS

Physical examination findings and clinical signs guide the selection of initial diagnostic tests. Lethargy, depressed appetite, and weight loss with or without abdominal organomegaly are found with many diseases. Nonspecific signs coupled with hyperglobulinemia may be consistent with a plasma cell neoplasm but more often are associated with infectious or immune-mediated disorders. However, nonspecific clinical findings in a middle-age to older cat with hyperglobulinemia should raise suspicion of MM.[4,5] Cats with localizable pain or neurological deficits can be evaluated further with plain survey radiography.

If MM is strongly suspected, the initial evaluation should include a complete blood count (CBC), platelet count or platelet estimate, serum biochemical panel, urinalysis, urine culture if indicated, serum and/or urine protein electrophoresis for monoclonal gammopathy, and abdominal radiographs and ultrasonographic evaluation. Spleen and liver fine-needle aspirate cytology examination should be performed if abnormalities are identified. Because soft tissue dissemination is common in cats at the time of initial presentation, evaluation of fine-needle aspiration cytology may be all that is required for a definitive diagnosis of malignant plasma cell tumor. A complete skeletal radiographic survey is warranted if a soft tissue mass amenable to fine-needle aspiration is not identified. Lytic, punched-out lesions may be evaluated via fine-needle aspiration or bone biopsy for tumor cell infiltration. Finding greater than 20 per cent plasma cells (particularly with morphological abnormalities) with bone marrow aspiration cytology and core bone biopsy confirms a diagnosis and aids in the clinical staging of plasma cell neoplasm. Most cats with malignant plasmacytosis in the bone marrow do not have lytic skeletal lesions radiographically, perhaps because they are too small to be detected, or because feline malignant plasma cells do not influence the bone marrow microenvironment sufficiently to cause significant lysis.

Myeloma proteins generally are greater than 160,000 MW (IgG) and cannot be filtered by the intact glomerular membrane. Because of their large size, they are restricted to peripheral blood and extracellular fluid. Serum protein electrophoresis is sufficient to identify a narrow band or "spike" of homogenous protein in the gamma globulin region, called a monoclonal gammopathy. Identification and quantification of excess intact immunoglobulin are determined easily with serum or urine immunoelectrophoresis and may be helpful in determination of the contribution of serum hyperviscosity to the clinical signs for which the cat is presented (Figure 62-2).

In healthy animals, heavy and light chain portions of the immunoglobulin typically are secreted together to form a normal, intact immunoglobulin. Malignant plasma cells can secrete an excess of light and/or heavy chains leading to increased immunoglobulin components in the peripheral blood. Free L chains are called Bence-Jones proteins. They are difficult to detect in peripheral blood but are sufficiently small (20 MW) to be filtered by the glomerulus and measured in urine by their ability to precipitate and dissolve at specific temperatures. The commercial urine dipstick is selective for albumin and fails to detect light-chain proteinuria. Bence-Jones proteinuria is detected in 20 per cent of human patients with MM without other evidence of disease.[15] In a case summary of 24 cats, about 70 per cent of patients tested for Bence-Jones proteinuria had detectable protein.[16] Urine protein electrophoresis is more sensitive than Bence-Jones protein determination, however.[15] Urine protein electrophoresis to detect monoclonal gammopathy is readily available, and should be sufficient to confirm the presence of a paraprotein.

Blood hyperviscosity primarily is a function of the concentration, size, shape, and protein-protein in addition to cell-cell interactions of individual proteins in solution. In human beings, the degree of serum hyperviscosity does not correlate well with clinical signs.[15] Hyperviscosity is measured rarely in cats and dogs. Viscosity, measured by comparing the flow time of serum to the flow time of water in a manual red cell pipette, has been described by Forrester, Greco, and Reform.[17] Myeloma protein in most cats is IgG, but IgA, IgM, and biclonal immunoglobulin production have been documented.[4,5] In general, larger immunoglobulins (IgM, IgA) should be more problematic because of their ability to aggregate and form high molecular weight complexes in solution; however, the sensitivity of individual cats to the effects of a specific protein concentration appears to be variable. Although relatively small, secreted IgG is the most common cause of MM-induced hyperviscosity syndrome in cats.[4,5] Excessive immunoglobulin may interfere with the coagulation cascade, or the antibody may inactivate specifically a protein required for hemostasis and thus prevent effective platelet function. Prothrombin time (PT) and partial thromboplastin time (PTT) were prolonged, and/or clot retraction was abnormal in dogs with MM and should be evaluated in all cats with uncontrolled bleeding.[4]

The criterion for diagnosis of MM in dogs and human beings requires that at least two of the following must be identified: osteolytic lesions, bone marrow plasmacytosis (greater than 20 per cent), a monoclonal gammopathy, and light chain proteinuria (Bence-Jones proteinuria).[1,4] Because cats seldom have osteolytic lesions, combined with a current lack of a commercially available assay for Bence-Jones proteins, our ability to make this diagnosis is limited. Histological or cytological evidence of malignant plasma cell neoplasm in soft tissue or bone with confirmation of a monoclonal gammopathy in plasma or urine by protein electrophoresis should be sufficient for a diagnosis of MM in cats.

Infectious (ehrlichiosis, FIP) and inflammatory causes of hyperglobulinemia should be pursued if a histologically confirmed plasma cell tumor or bone osteolysis cannot be identified. The polymerase chain reaction (PCR) test has been used to confirm *Ehrlichia canis*–like infection in three cats.[18] Currently, no standardization exists among laboratories providing an *Ehrlichia* spp. serologic test for use with cat sera; therefore PCR may be needed for diagnosis.[18] The availability of PCR is limited, however. Cats with clinical findings referable to ehrlichiosis and seroreactivity to *Ehrlichia* antigens should be considered infected. Diagnosis of FIP requires careful assessment of clinical and laboratory findings, along with histological confirmation. Evaluation for nonspecific signs of weakness, lethargy, and inappetence should include a serum thyroxine (T_4) measurement. Blood pressure determination can be used to further evaluate hypertension as a cause of bleeding diathesis and should be performed in all cats with renal insufficiency.

Because most cats with plasma cell tumors are older and many may be systemically ill with diseases unrelated to MM, additional tests for viral disease (FeLV and FIV enzyme-linked immunosorbent assay [ELISA]), infectious hemoparasites

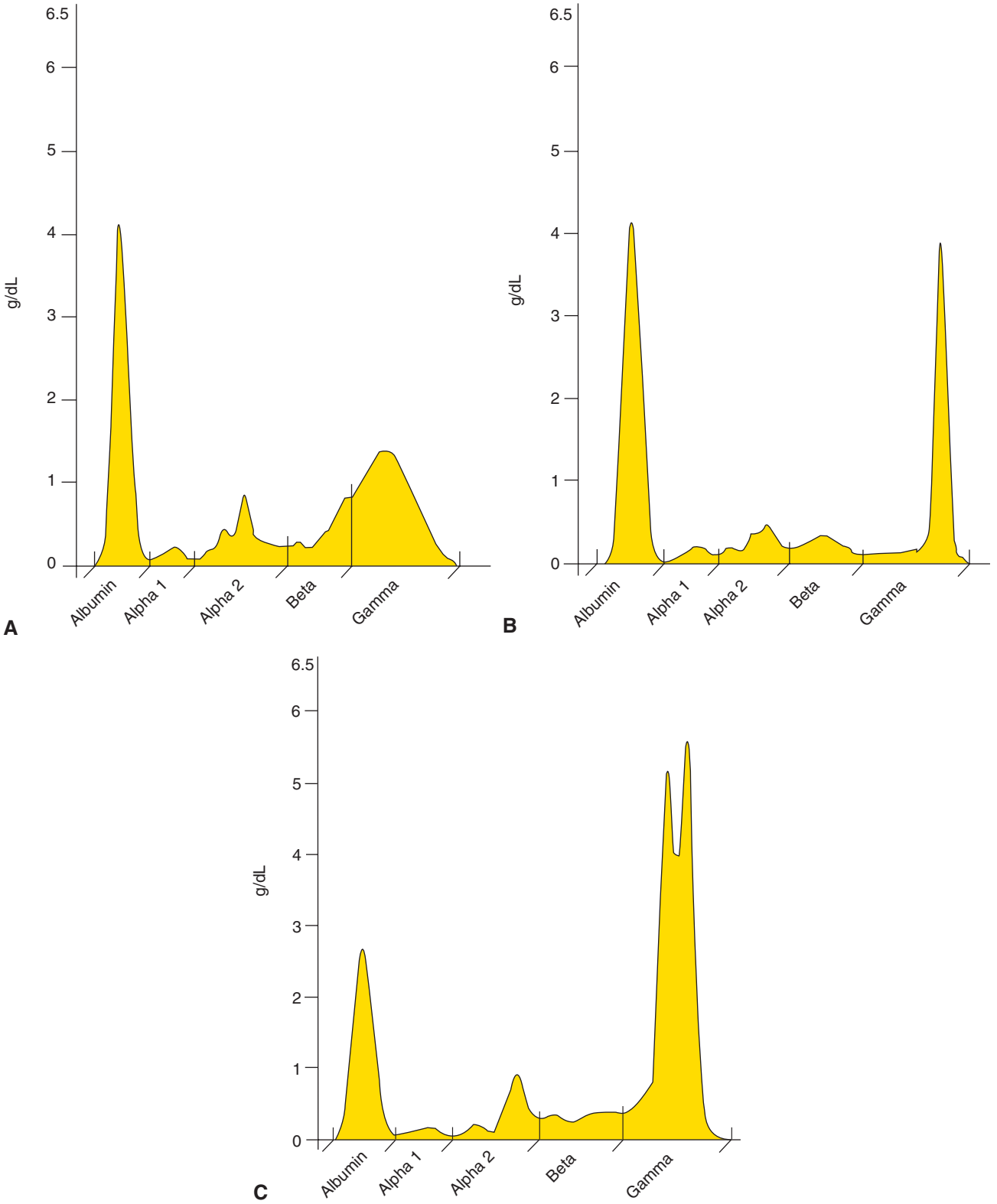

Figure 62-2. Serum protein electrophoretograms. **A,** A polyclonal gammopathy characterized by an increase in a variety of immunoglobulin classes associated with an immune response. This pattern would be suggestive of chronic inflammatory or infectious disease. **B,** Electrophoretogram of a cat with multiple myeloma showing a monoclonal spike in the gamma globulin region demonstrating overproduction of a single class of immunoglobulin. **C,** In a biclonal gammopathy, the gamma globulin fraction is increased, characterized by two narrow spikes from two distinct plasma cell clones with each producing a unique immunoglobulin class. This pattern may be associated with multiple myeloma.

(*Mycoplasma* spp. [hemobartonella] PCR), hyperthyroidism (T_4), renal insufficiency (including blood pressure measurement), and coagulopathies (PT, PTT, and D-dimer) may help identify serious concurrent disease.

The definitive diagnosis of a plasma cell tumor is determined from cytological examination of a bone marrow aspirate or histological confirmation. Grossly, the marrow is gelatinous and soft, with red areas that originate intramedullary and eventually erode cancellous bone and then the bony cortex. Microscopic evaluation of the marrow reveals increased number of plasma cells, typically greater than 20 per cent. They can be infiltrative diffusely or present in sheetlike clusters. Many neoplastic plasma cells look like their benign counterparts with a perinuclear clear area and an eccentrically placed nucleus. Malignant plasma cells also may have multiple nucleoli, prominent nucleoli, cytoplasmic vacuoles containing immunoglobulin, increased numbers of mitotic figures, bizarre mitotic figures, and multiple nuclei (Figure 62-3).

With the exception of hyperproteinemia and hyperglobulinemia, clinical laboratory findings are variable and nonspecific. In the VCOG study, hyperbilirubinemia, increased ALT activity, and hypoalbuminemia were found in almost one half of the cats.[5] A direct effect of plasma cell infiltrate of the liver, an indirect effect of hypoxia resulting from serum hyperviscosity, and hepatic lipidosis from decreased food intake all may be responsible for leakage enzyme activity and evidence of cholestasis in some cats. The hypoalbuminemia may be due to decreased production (hepatic insufficiency, malnutrition), increased loss (glomerulopathy), or as a consequence of changes in serum oncotic pressure related to hyperglobulinemia. Hypercalcemia was rare, which reflected infrequent osteolysis with MM.[4,5] Hypercalcemia is thought to be caused by osteoclast-activating molecules such as interleukin-6 and interleukin-1 beta by bone and stromal cells.[1]

Cytopenias caused by myelophthisis and plasma cell–induced changes in the bone marrow microenvironment are reflected in abnormal hematological values. Anemia is the most common hematological abnormality in dogs, cats, and human beings with MM.[4,5,15] Most anemias detected in cats with MM are normocytic, normochromic, and nonregenerative. Thrombocytopenia is common because of decreased platelet production and increased use in formation of capillary thrombi.

Some affected cats have evidence of hemoconcentration, azotemia, electrolyte disturbances, and low urine specific gravity consistent with renal insufficiency. Additionally, proteinuria may be detected. Renal injury may result from failure of tubules to metabolize individual light chains, which leads to kidney damage from light chain tubular cast–induced interstitial nephritis and/or by light chain or amyloid deposition within the glomerulus. Damage may be exacerbated by dehydration, serum hyperviscosity, infection, and hypercalcemia-related tubular unresponsiveness.[15]

Radiographic skeletal survey may be helpful in diagnosis of MM. However, lytic bone lesions are less frequent in cats than in human beings or dogs. Detection of malignant plasma cells via bone marrow aspirate cytology in the absence of osteolytic lesions is common in cats.[5] Bone lesions result from increased osteoclastic bone resorption that occurs adjacent to the myeloma cells as a result of locally acting factors produced by myeloma cells. New bone formation that occurs normally at the site of bone destruction is suppressed.[19] Survey radiography of the entire skeleton may be necessary, because lesions may be solitary and can be found in any bone of the appendicular or axillary skeleton. The bone lesions appear radiographically as punched-out defects, usually 0.5 to 1 cm in diameter (Figure 62-4). Bone scintigraphy and IV technetium-99m-methylene disphosphonate scans may help to identify active regions of plasma cells within bone.[20] When trying to confirm whether a plasmacytoma is solitary, magnetic resonance imaging (MRI) and computerized tomography (CT) provide greater details of bone marrow and bone disease often not detected by plain radiographs.[21] MRI may be particularly useful to assess tumor burden in cats, because bone marrow frequently is affected without evidence of osteolysis.

Plain radiography can be used to evaluate the thorax and abdomen directed by clinical and physical findings. Abdomen radiography frequently reveals organomegaly (Figure 62-5). Although ultrasonographic findings of hepatomegaly and/or splenomegaly are common, echotexture is not diagnostic and may consist of hyperechogenic, hypoechogenic, and normoechogenic parenchyma[22] (Figure 62-6).

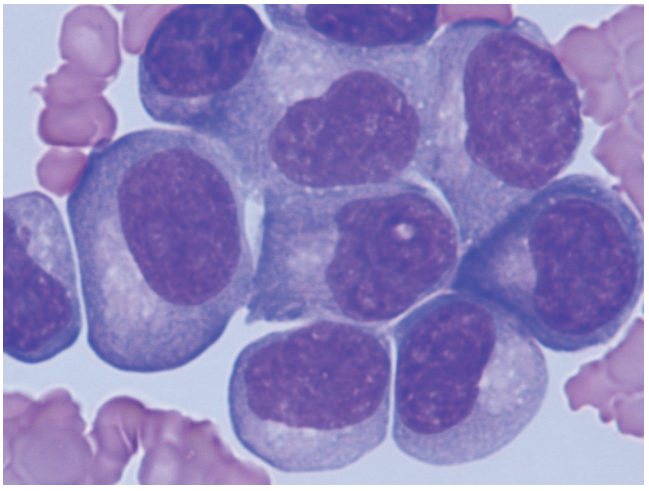

Figure 62-3. A population of malignant plasma cells from the splenic aspirate of a cat with multiple myeloma. The plasma cells present are characterized by an eccentrically located nucleus with clumped chromatin, a deeply blue cytoplasm, and a prominent perinuclear clear zone (Golgi zone). (Wright-Giemsa stain, 100×). (Photo courtesy C.W. Brockus.)

Figure 62-4. Lateral views of the left and right stifles of a cat with multiple myeloma. In the distal femoral metaphysis and in the right proximal tibia, moth-eaten bone lysis is noted with periosteal new bone formation. Bone biopsy histopathological findings indicated malignant plasma cell proliferation consistent with multiple myeloma. (Photo courtesy J. Locke.)

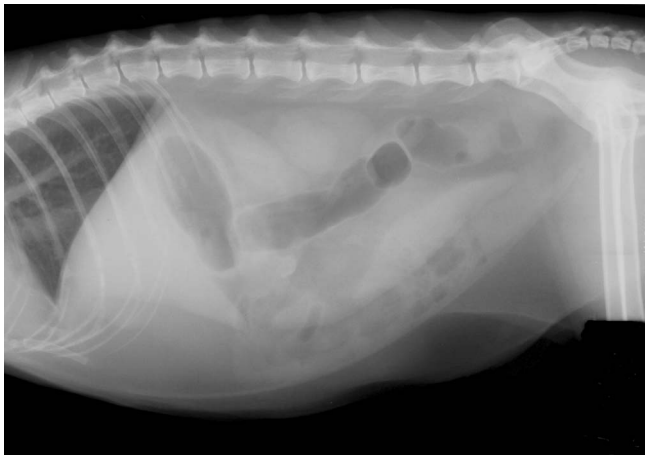

Figure 62-5. In this lateral abdominal radiograph, hepatosplenomegaly is evident as the liver extends beyond the costal arch and displaces the stomach caudally, and the spleen is prominent with rounded margins. (Photo courtesy M.D. Winter.)

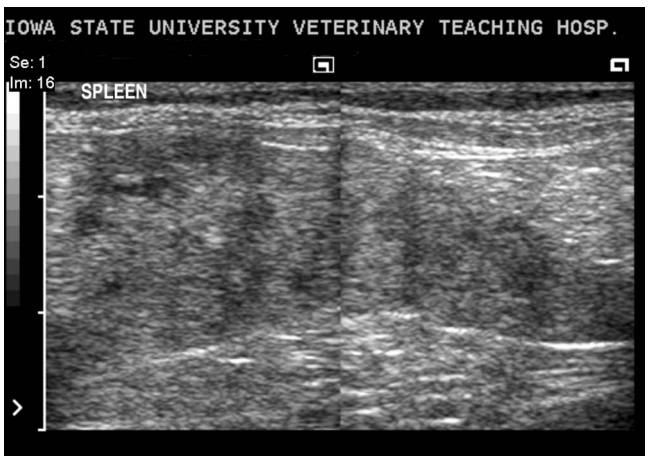

Figure 62-6. Composite image (two scans) of the spleen was obtained with a 10-MHz linear transducer. The spleen is enlarged and the splenic parenchyma is mottled and heterogeneous. (Photo courtesy M.D. Winter.)

TREATMENT

The goal of treatment is to slow the proliferation of malignant plasma cells and to control the adverse clinical signs associated with direct effects of tumor expansion and/or high serum globulin concentrations. Therapy with melphalan and prednisone was introduced in the 1960s for human patients with MM and has been changed little since then.[23] Melphalan (L-phenylalanine mustard) (Alkeran, Burroughs Wellcome Co., Research Triangle Park, NC), an alkylating agent, and prednisone have been accepted as standard treatment for MM in human beings and dogs but are not as efficacious in cats.[1,2,4] Melphalan is given (0.1 mg/kg or 1.5 mg/m^2 PO daily for 10 days, then 0.05 mg/kg or 1.5 mg/m^2 daily) with prednisone 0.5 mg/kg (30 mg/m^2) PO daily for 21 days, then every other day thereafter, or as a single agent at 2 mg/m^2 PO for 10 days followed by no therapy for 2 to 3 weeks.[2,4] Treatment with prednisone (Deltasone, The Upjohn Co., Kalamazoo, MI) alone results in only short-term response in the few cats reported and those I have treated.[4,22] Therapy is continued in human patients for at least 1 year.[15]

Melphalan is well tolerated and few adverse effects (e.g., myelosuppression and occasionally inappetence and vomiting) are experienced by cats. A CBC and a platelet count or platelet estimate should be monitored every week for the first 4 weeks of therapy and every 2 weeks thereafter. Thrombocytopenia is a common consequence of long-term melphalan therapy and may precede neutropenia. Myelosuppression most commonly is seen 3 to 6 months after starting therapy. In my experience, discontinuation of melphalan for 2 to 3 weeks allows resolution of thrombocytopenia, but complete cessation of therapy for prolonged periods encourages or allows for disease progression. Prednisone therapy should be continued. Cyclophosphamide (Cytoxan, Mead Johnson, Evansville, IN) is relatively platelet sparing and could be used for replacement of melphalan. A 25 per cent dose reduction or discontinuation of melphalan allows resolution if significant neutropenia ensues. Neutrophil counts should return to normal within 4 to 7 days after discontinuing melphalan. Weekly CBCs are indicated to assess changes. Chlorambucil (Leukeran, Glaxo Smith-Kline, Research Triangle Park, NC) may be substituted if persistent neutropenia is problematic; however, the efficacy of this drug for MM in cats currently is undetermined.

Dogs and cats with recalcitrant or relapsing MM may be treated with cyclophosphamide or with multidrug protocols used for the treatment of lymphoma, containing vincristine, doxorubicin, and prednisone, although little information exists about their efficacy.[2,6] In people, most combination chemotherapy protocols offer minimal improvement when compared with a melphalan and prednisone combination.[15]

The addition of lomustine (CeeNu, Bristol-Myers Oncology, Plainsboro, NJ) has been helpful in human patients with refractory MM.[24] A well-tolerated, effective dose of lomustine has not been determined for cats. However, one cat with MM treated with lomustine (10 mg/cat, PO every 4 weeks) achieved a partial remission with three doses combined with daily oral prednisone at an anti-inflammatory dose.[25] In a recent study of 20 cats, a low rate of lomustine hematological toxicity was reported associated with a dosage of 10 mg/cat (translated into 32 to 59 mg/m^2). These observations imply that the maximum tolerated dosage probably was not reached and that the therapeutic benefit may be improved with higher doses.[25]

Appropriate markers of response to therapy have not been identified for cats. However, improvement in clinical signs or quality of life is a useful indicator. Pain relief, increased patient activity, and appetite are good subjective signs of a response.[15] Stabilization of disease (or a partial response), and a decrease in serum or urine myeloma protein concentration, is an objective measurable response to cytotoxic chemotherapy. Improvement in clinical signs (3 to 4 weeks) has been reported to precede the decrease in serum protein concentrations (3 to 6 weeks).[26] Clinical response was judged complete when serum concentrations of monoclonal immunoglobulin were undetectable and partial, when a 50 per cent decrease occurred in 60 dogs with MM.[6] In human beings, the concentration of myeloma protein roughly parallels the size of the tumor mass, so a decrease in concentration reflects control of plasma cell proliferation.[15] Relapse may be detected early by making serial serum globulin or total protein concentration determinations. Reappearance of a monoclonal gammopathy on follow-up electrophoretogram signals tumor progression. Complete repair of osteolytic lesions is rare in human beings, dogs, and cats.[4,15,27]

In a report of dogs with MM, retinal detachment with loss of vision was reversed in three of four eyes after remission was achieved with melphalan/prednisone.[28]

Bisphosphonates, potent inhibitors of bone resorption, are used to treat MM-associated hypercalcemia, reduce the incidence of skeletal lesions, alleviate bone pain, and improve quality of life. Pamidronate, a second-generation amino-bisphosphonate, has been evaluated in a randomized, double-blind trial in human patients with MM.[19,29] Bone pain and analgesic requirement were reduced significantly in the pamidronate group, and skeletal lesions and episodes of hypercalcemia were reduced by half. Survival was prolonged in poor-prognosis patients who failed to respond to first-line chemotherapy. Although a therapeutic benefit of bisphosphonates is undetermined in cats, 1.2 mg/kg pamidronate disodium (Pamidronate disodium, Novartis, Basel, Switzerland) diluted in 25 ml normal saline infused over 2 hours has been administered intravenously once monthly without adverse effects to a cat with oral squamous cell carcinoma. After three doses, renal function remained normal, based on normal serum biochemistry values and concentrated urine specific gravity.[30] A single dose of pamidronate was given safely at a dosage range of 1.5 to 2.0 mg/kg IV to two cats with nonneoplastic hypercalcemia. Total serum calcium or ionized calcium returned to normal concentration within 48 hours. The duration of effect was 9 weeks in one cat and is apparently unrelated to the dose given.[31]

Solitary extramedullary soft tissue plasmacytomas should be removed if amenable to surgical excision. Most have an aggressive clinical course; therefore surgical excision is unlikely to be curative.[4,32] Surgical excision could be valuable for tumor debulking to improve response to radiation therapy and/or chemotherapy and for palliation.

Radiation therapy for solitary or multifocal bone lesions or soft tissue plasmacytomas is warranted for palliation or local control but remains largely untried. Local radiation combined with high-dose dexamethasone therapy is palliative treatment for focal lesions in human beings and may be helpful for cats with painful osteolysis.[33] Two cats with solitary oral plasmacytomas involving bone of the maxilla or mandible were treated with surgical excision and radiation therapy with chemotherapy. One is still alive approximately 9 months after surgical excision and the other survived 3.9 years.[22] In another study, combination therapy with dorsal laminectomy, local irradiation, and chemotherapy achieved control of a compressive solitary osteolytic vertebral lesion, allowing survival of nearly 2 years in one cat.[34]

MANAGEMENT OF COMMON COMPLICATIONS

Complications must be managed simultaneously with the institution of cytotoxic chemotherapy if possible. Immunosuppression with secondary localized and systemic infections is a result of hyperproteinemia and defects in B-cell and T-cell function. It is common in symptomatic myeloma. Humoral immunity is affected more than cell-mediated immunity in human patients with myeloma.[15] Production and function of normal immunoglobulins are depressed. When abnormal immunoglobulin production is controlled, normal immunoglobulins are reestablished, long-term prognosis is improved, and infection rate is less frequent. Development of renal failure and the addition of cytotoxic chemotherapy further exacerbate defective immune responses.[23] Serious concurrent bacterial infections in cats also have been reported.[4]

Management of microbial infections includes prevention of disease by isolating cats with MM from nonvaccinated or sick cats, antibiotic prophylaxis, and vigilant monitoring for secondary infections. Human myeloma patients exhibit a poor antibody response to pneumococcal and influenza vaccines.[23] Whether routine vaccination of cats will be an effective management strategy for cats with MM is undetermined. Recurrent bacterial infections can be controlled with aggressive bactericidal antibiotic therapy, but nephrotoxic antibiotics must be avoided. Febrile neutropenic cats should be hospitalized for intravenous antibiotic therapy (see Chapter 69).

Proposed causes of anemia are myelophthisis, cytokine-induced apoptosis of immature erythrocytes, and inappropriate levels of erythropoietin.[15] Recombinant human erythropoietin has been shown to decrease the transfusion requirements significantly and to improve the quality of life and performance status in anemic people with MM, even patients with mild anemia.[35] Recombinant human erythropoietin may be valuable in the management of anemic MM cats. A whole blood transfusion or packed red blood cells may be needed for symptomatic anemia. Careful assessment of the patient during the transfusion is necessary to avoid volume overload (see Chapter 69).

Adequate hydration improves blood viscosity, blood circulation, and coagulation, decreases hypercalcemia, and helps to maintain kidney perfusion and function while it increases abnormal protein excretion. Azotemia should improve with administration of fluid therapy and concurrent cytotoxic therapy. Exacerbation of volume overload leading to overt heart failure may limit initial aggressiveness of therapy. Adequate nutrition is needed because most cats are underweight at the time of presentation for MM.[2,4] Response to therapy is better, and adverse effects are less frequent, when adequate body weight and nutrition are maintained (see Chapter 16). Vomiting and inappetence secondary to cytotoxic drug therapy may be problematic initially, however.

Effective chemotherapy decreases the production of paraproteins, but this effect is gradual over days to weeks with slow decrease in clinical signs.[26] Plasmapheresis can be helpful when rapid resolution of clinical signs is needed.[3] Because a small decrease in plasma paraprotein concentration results in a large decrease in plasma hyperviscosity, a single plasmapheresis may be sufficient to alleviate clinical signs of hyperviscosity syndrome.[36]

The availability of continuous plasmapheresis is limited to referral institutions; however, intermittent plasmapheresis has been described for the management of plasma hyperviscosity in dogs and cats and is a straightforward procedure.[3] Briefly, 30 to 50 ml of whole blood (10 to 15 ml/kg body weight) can be collected from the patient in transfer packs with anticoagulant and centrifuged to separate plasma and cells. The cells then are resuspended in normal saline and administered intravenously back to the patient. One plasma exchange usually is sufficient to manage clinical signs, but the procedure may be repeated every 2 weeks if needed.[3]

PATHOLOGICAL FINDINGS

Bone marrow aspirate cytology and biopsy obtained via Jamshidi needle (18-gauge) is useful in determination of the

extent of bone marrow involvement and assessment of the degree of plasma cell dysplasia. Immunohistochemical staining of a biopsy sample for cytoplasmic light chains (κ and λ light chains) helps to identify malignant plasma cells and to demonstrate that they are a homogenous population of monoclonal cells distinct from reactive plasma cells.[10] Newer techniques, such as assessment of quantity of aberrant plasma cells, plasma cell labeling index using flow cytometry, B2 microglobulin, and bone marrow microvessel density, are valuable for predicting prognosis in human patients and may be helpful in the future in identification of cats likely to respond to therapy.[37]

PROGNOSIS

When individual case reports of cats with MM were evaluated by Ogilvie and Moore, a 4-month to 12-month range in survival time with a variety of treatments was described.[4] In the VCOG study involving 27 cats, the overall median survival time was 87 days (range, 1 day to 1,395 days).[5] The average survival time of cats treated with combination melphalan and prednisone was 183 days, if they survived 2 weeks after diagnosis. A 27 per cent response rate with no complete remissions was reported.[4] This is in sharp contrast to the 540-day median survival time and more than 90 per cent response rate reported for 60 dogs with MM.[6]

In human beings, increasing melphalan and dexamethasone dosages are associated with a better clinical response and longer survival.[1] Melphalan typically is formulated in 2-mg tablets, which makes cat body surface area–specific dosing impossible without drug reformulation. Treatment with exact therapeutic prescribed doses may improve survival times and response to therapy.

Prognosis for cats with solitary plasmacytomas varies with biological behavior and aggressiveness of therapy. Solitary extramedullary plasmacytomas are uncommon, and low case numbers make it difficult to predict their biological behavior reliably. In a recent study of extramedullary plasmacytomas, nine cats could be classified according to the system for dogs, but clinical outcome was undetermined.[10] Future studies may elucidate the relationship between histological grade and biological behavior, which makes therapy selection and prognosis more evident.[38] Exceptionally long survival times of almost 2 years have been reported in rare cases of focal osteolytic plasmacytomas treated with therapy combinations of surgical reduction and chemotherapy with or without radiation therapy.[16,22] Progression of disease appears inevitable for almost all cats with extramedullary plasmacytomas.[34]

In human beings, clinical stage of disease is based on the estimated plasma cell mass, bone osteolysis, paraprotein and hemoglobin concentrations, renal function, and the presence of hypercalcemia. Clinical stage then is predictive of survival and response to therapy.[39] When applied to 60 dogs with MM, clinical stage was not predictive of long-term survival.[6] A cat-specific clinical staging system is needed, because disseminated soft tissue involvement is more common than bone osteolysis, and hypercalcemia and renal insufficiency are associated uncommonly.

Variables associated with a better prognosis in dogs have been identified as treatment (versus no treatment), the addition of cyclophosphamide to melphalan and prednisone therapy (afforded improved survival), normal serum calcium concentration, absence of light chains of myeloma protein in the urine, and few bony lesions. These prognostic variables were correlated with significantly better median survival times. Gender, monoclonal Ig class, clinical stage, increased serum viscosity, and azotemia did not correlate significantly with prognosis in dogs.[6] Similarly, cats treated with chemotherapy lived significantly longer than untreated cats (137 days versus 4.5 days); however, the significance of other prognostic variables remains undetermined.[5]

Malignant plasma cell proliferation is controlled by growth and survival signals from supporting cells in the bone marrow microenvironment. Although high-dose melphalan with autologous bone marrow stem cell transplantation is now considered standard therapy for MM in young human patients, newer therapies are directed at control of the bone marrow cells that perpetuate malignant plasma cell proliferation.[19] New active drugs include immunomodulatory agents, such as thalidomide and lenalidomide, and proteasome inhibitors (bortezomib) that act directly on myeloma cells and indirectly by suppressing supporting cell interactions.[40] Cats with MM hopefully will benefit from some of these and other new therapies in the future.

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Chapter 63

Update on Hemoplasmosis

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CLASSIFICATION

The gram-negative erythrocytic bacterium *Haemobartonella felis,* until recently, was classified as a rickettsial organism. However, data regarding the DNA sequences of different *Haemobartonella* isolates have revealed that actually it is more closely related to the genus *Mycoplasma*.[1,2] Studies also have documented the existence of two morphologically and genetically distinct *H. felis* genotypes. These genotypes have been named by some as the large or Ohio form and the small or California form[1,3-5] and actually represent distinct species. Reclassification and renaming of these species as mycoplasmal organisms has occurred recently,[6-8] with renaming of *H. felis* species as *Mycoplasma haemofelis* (for the large form) and "*Candidatus* Mycoplasma haemominutum" (for the small form). These two species are now collectively referred to as the feline hemoplasmas. Work recently published suggests that a third pathogenic feline hemoplasma organism exists in Switzerland.[9] Further sequencing work is required to further define this isolate but it appears to be closely related to a rodent hemoplasma species.

PATHOGENESIS OF THE FELINE HEMOPLASMAS

Induction of Anemia

The attachment of the hemoplasma to erythrocytes results in direct damage to the erythrocytic membrane, which leads to a shortened erythrocyte lifespan. Erythrocyte damage also may induce the production of anti-erythrocytic antibodies, or antibodies may arise directed against the hemoplasma organism itself, resulting in erythrocytic destruction as an "innocent bystander." Positive Coombs' tests and autoagglutination have been reported in cases of acute hemoplasmosis,[10-12] which indicates the presence of erythrocyte-bound antibodies. We and others have demonstrated the development of cold-reacting (IgM) antibodies in hemoplasma-infected cats[13,14] during periods of anemia. In our experimental studies, these antibodies have disappeared after resolution of the hemoplasma-induced anemia. The majority of hemolysis in hemoplasma infection is extravascular in nature, although severe intravascular hemolysis has been reported in a Swiss cat with the recently described novel feline hemoplasma species.[9] Splenic macrophages may remove hemoplasma organisms from the erythrocyte surface and return unparasitized cells into circulation. This may explain the rapid increase in packed cell volume (PCV) seen in some cases after the clearance of organisms from the circulation. Recent experimental and prevalence studies have shown differences in pathogenicity between the two feline hemoplasma species.

"Candidatus M. haemominutum"

In recent studies, experimental infection of cats with different isolates of "*Candidatus* M. haemominutum"[4,15] did not result in significant clinical signs, and significant anemia was not induced. In agreement with this, studies that evaluated natural hemoplasma infection in the United Kingdom[16] and United States[17] found no statistical difference in the prevalence of anemia between cats that tested positive and negative for "*Candidatus* M. haemominutum." One recent study[18] evaluated the pathogenicity of "*Candidatus* M. haemominutum" in retrovirus-infected and non–retrovirus-infected cats. In this study, a mild or moderate transient decrease in hemoglobin concentration with "*Candidatus* M. haemominutum" infection occurred in seven of nine non–retrovirus-infected cats, in addition to the development of a more severe anemia in those cats that were retrovirus (feline leukemia virus [FeLV] alone or FeLV and feline immunodeficiency virus [FIV]) infected. A recent Australian study[19] of naturally infected cats also found that cats that tested positive for "*Candidatus* M. haemominutum" had significantly lower hematocrit values than cats that tested negative for "*Candidatus* M. haemominutum," although the retrovirus status of these cats was not determined. Further work is required therefore to ascertain the true degree of pathogenicity of this organism in cats.

Mycoplasma haemofelis

Experimental infection with *M. haemofelis*, on the other hand, usually results in a severe, sometimes fatal, hemolytic anemia.[3,4,15] A prevalence study in the United States[17] found that

anemic cats were more likely to be infected either with *M. haemofelis* or with "*Candidatus* M. haemominutum" and *M. haemofelis* than nonanemic cats, which supports the experimental study results that *M. haemofelis* induces anemia. However, prevalence studies in Australia[19] and the United Kingdom[16] have failed to demonstrate a consistent association between anemia and *M. haemofelis* infection. Variation in the results obtained in these different studies is likely to be due partly to the numbers of cats involved and the type of cats sampled. For example the United States study by Jensen[17] included a significant number of cats recruited into the study because feline hemoplasma infection was suspected based on clinical signs and hematological and cytological features. This study therefore probably selected for cats more likely to have clinical *M. haemofelis* infection. In contrast, the Australian[19] and United Kingdom[16] studies consisted primarily of cats having blood samples taken for routine hematology for any sign of ill health, in addition to some healthy cats, and thus probably are more likely to have sampled more asymptomatic chronically *M. haemofelis*–infected cats.

In Vivo Kinetics of Hemoplasma Infection

A recently developed quantitative real-time polymerase chain reaction (PCR) assay[20] has allowed quantification of hemoplasma copy number in infected cats. Accurate quantification of hemoplasma infection had not been achieved previously because of the uncultured status of the hemoplasmas. Such quantitative real-time PCR studies have allowed further insight into the pathogenicity of "*Candidatus* M. haemominutum" and *M. haemofelis*. Graphs depicting examples of hemoplasma copy number measurements in infected cats are shown in Figure 63-1. Cats infected with both hemoplasma species initially show a rapid increase in copy number, with peak numbers typically reached after around 2 to 4 weeks. However, *M. haemofelis* copy numbers can fluctuate greatly even within the initial postinfection period. Some *M. haemofelis*–infected cats continue to have large changes in *M. haemofelis* copy numbers for several months after experimental infection. In contrast, cats infected with "*Candidatus* M. haemominutum" show less fluctuation in copy numbers, although a slight reduction in copy number often is seen after the peak number is reached. The greater pathogenicity of *M. haemofelis* may induce a greater immune response in the host and contribute to the large fluctuations in copy number seen in some *M. haemofelis*–infected cats.

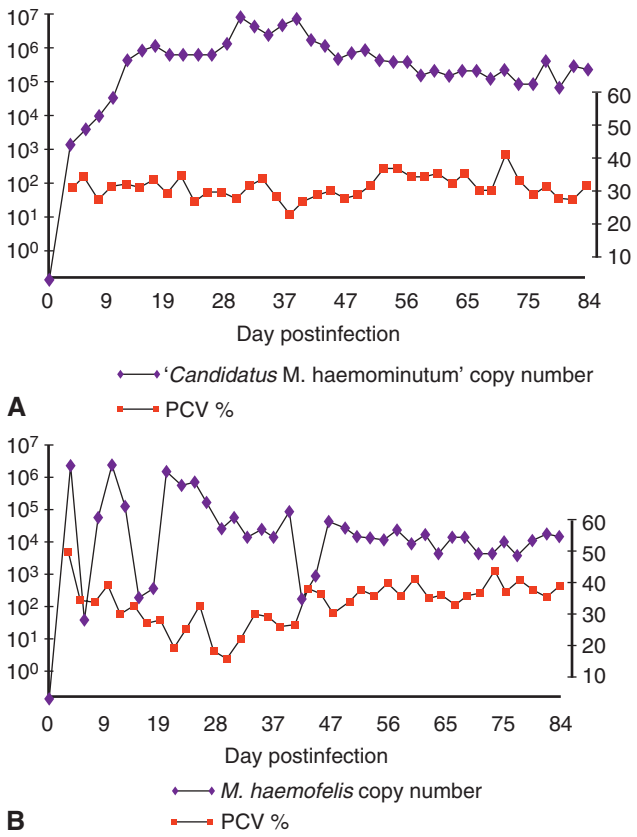

Figure 63-1. Graphs showing examples of hemoplasma copy number variation over time after experimental infection. Hemoplasma copy number has been measured using a real-time quantitative PCR assay (based on the 16S rDNA gene) and values are shown on the y-axis with time postinfection on the x-axis. PCV values at each timepoint also are shown. **A,** "*Candidatus* M. haemominutum" copy number variation with time. **B,** *M. haemofelis* copy number variation with time. The copy numbers shown relate to the number of copies present per microliter of blood, if 100 per cent efficiency of both the DNA extraction and PCR amplification is assumed. To relate copy numbers to hemoplasma organism numbers, the number of 16S rDNA sequences present in the hemoplasma genome being amplified also must be considered. Currently mycoplasma species are believed to contain either one or two copies of 16S rDNA sequences. Thus true organism numbers could be half of the copy numbers shown in these graphs.

CARRIER STATUS

Cats that recover from infection may remain chronically infected with hemoplasmas for an undetermined period of time, which may be a lifetime in some cases. Previously, the carrier status was believed to occur when cats were allowed to recover from infection without antibiotic treatment,[21] but a recent study has detected chronic infection by PCR assays in cats up to 6 months after initial infection, despite doxycycline treatment.[3] Parasitemia generally is not visible on blood smears during this period and such cats usually are clinically normal with a normal hematocrit. These cats appear to be in a balanced state in which replication of organisms is matched by phagocytosis and removal, although reactivation of infection can occur and may result in clinical disease.[4] An increase in the level of parasitemia has been documented in carrier cats given corticosteroids[3,21] but clinical disease was not seen. Unpublished studies at the University of Bristol have found that long-term carrier status is encountered more commonly with "*Candidatus* M. haemominutum" infection compared with *M. haemofelis*. We have found that cats infected with *M. haemofelis* can become PCR-negative spontaneously on repeated blood sampling months after stopping antibiotic treatment, whereas cats infected with "*Candidatus* M. haemominutum" remain strongly positive by PCR for months or years after infection.

EPIDEMIOLOGY

Prevalence

Recent prevalence studies using PCR for diagnosis of feline hemoplasma infection in the United States,[17,22] the United Kingdom,[16] and the Sydney area of Australia[19] are summarized in Table 63-1. These studies found a relatively high prevalence

Table 63-1 | **Results of Feline Hemoplasma Prevalence Studies in the United States, United Kingdom, and Australia Using PCR for Diagnosis**

	U.S. CLIENT-OWNED CAT STUDY[17]	U.K. CLIENT-OWNED CAT STUDY[16]	U.S. (NORTHERN FLORIDA) FERAL CAT STUDY[22]	AUSTRALIAN (SYDNEY AREA) CLIENT-OWNED CAT STUDY[19]
Total number of cats in study	220	426	484	147
Per cent cats positive for *"Candidatus* M. haemominutum*"* alone	12.7 per cent	16.9 per cent	8.3 per cent	23.1 per cent
Per cent cats positive for *M. haemofelis* alone	4.5 per cent	1.4 per cent	4.3 per cent	4.1 per cent
Per cent cats positive for *"Candidatus* M. haemominutum*"* and *M. haemofelis*	2.3 per cent	0.2 per cent	3.9 per cent	0.7 per cent

of infection with "*Candidatus* M. haemominutum," with *M. haemofelis* infection being less common and co-infection with both species rare. The greater prevalence of *"Candidatus* M. haemominutum" may be a reflection of the fact that long-term carrier status is thought to be common with this species.

Mode of Transmission

The epidemiology of hemoplasma infection is poorly understood. Experimental transmission has been demonstrated via the intravenous, intraperitoneal, and oral routes using infected blood. Although the cat flea *Ctenocephalides felis* has been incriminated in the transmission of hemoplasma species in cats, this remains unproven as a natural means of transmission. Preliminary studies have shown experimental transmission of "*Candidatus* M. haemominutum" from infected cats to *Ct. felis*, and the presence of "*Candidatus* M. haemominutum" DNA in feces, eggs, and larvae from infected fleas, although transmission of infection to a naïve cat was not achieved.[23]

A recent study performed in the United Kingdom[24] found that 48.9 per cent of flea samples collected from pet cats were positive for "*Candidatus* M. haemominutum" DNA, although no evidence of *M. haemofelis* DNA was found. In a similar study of fleas from 91 cats in the United States (Maryland, Texas, and Alabama), the prevalence rates for "*Candidatus* M. haemominutum" alone, *M. haemofelis* alone, and combined infection were 23.6 per cent, 1.1 per cent, and 1.1 per cent, respectively. These results suggest that fleas may well be involved in the transmission of feline hemoplasmas. The absence of any *M. haemofelis* DNA in the fleas from the United Kingdom and the small number of *M. haemofelis* positives in the fleas from the United States may reflect the small sample size of these studies in combination with the low prevalence of *M. haemofelis* infection in cats from these two countries.[16,17] Interestingly, experimental transmission of *M. haemofelis* infection between cats by the hemophagous activity of *Ct. felis* has been achieved, although attempts to transfer infection via ingestion of fleas, or flea products, failed.[25] Further investigation of the role of *Ct. felis* in the transmission of both hemoplasma species in cats is warranted.

Risk Factors

Male cats are more likely to be infected with "*Candidatus* M. haemominutum" or *M. haemofelis,*[16,19,22] and older cats are more at risk of "*Candidatus* M. haemominutum" infection,[16,19] which possibly reflects a cumulative risk of exposure to the organism with time. Nonpedigree cats are more likely to be infected with "*Candidatus* M. haemominutum" than pedigree cats.[16,19]

FeLV infection has been suggested to be a risk factor for hemoplasma infection; up to 47.2 per cent of hemoplasma infected cats are FeLV-positive.[26,27] A recent study of feral cats in the United States found that FeLV infection was associated with an increased risk of co-infection with "*Candidatus* M. haemominutum," but not *M. haemofelis,*[22] although a study of pet cats in the United Kingdom failed to show any association between FeLV-positive PCR status and either hemoplasma species.[28] Despite these conflicting studies, the FeLV status of any cat found to be hemoplasma infected should be checked.

An association between FIV and hemoplasma infection also has been proposed. In one study, 40 per cent of anemic FIV-positive cats were infected with hemoplasmas,[29] and FIV infection was associated with an increased risk of co-infection with "*Candidatus* M. haemominutum," and *M. haemofelis*, in the study of feral cats in the United States.[22] FIV PCR-positive status also was a significant risk factor for "*Candidatus* M. haemominutum" infection in a study in the United Kingdom,[28] but further evaluation of these data suggested that breed could have been a significant confounder on the apparent effect of FIV status on "*Candidatus* M. haemominutum" infection. In other words, an apparent association between FIV status and "*Candidatus* M. haemominutum*"* arose because both of these infections are more likely in nonpedigree cats rather than a direct effect of FIV. However, it cannot be ruled out that an association between FIV and hemoplasma infection exists, because both agents may be transmitted between cats by similar methods (e.g., catfights) or because the immunosuppressive effects of FIV infection enhance hemoplasma secondary infections. Therefore the FIV status of any hemoplasma-infected cat should be checked.

CLINICAL SIGNS

The clinical signs seen with hemoplasma infection depend upon a number of factors, such as the species involved, stage of infection, and the degree and speed of development of any anemia. Common clinical signs seen in ill cats include anorexia, lethargy, dehydration, weight loss, and depression. Intermittent pyrexia is seen commonly, particularly in the acute stages of disease, in addition to splenomegaly, which may

reflect extramedullary hematopoiesis. Icterus is seen occasionally but is uncommon. Some studies have suggested that concurrent FeLV or FIV infection may worsen clinical disease because of hemoplasmosis,[18,30-33] although detailed hematological data were not always presented. A recent experimental study at the University of Bristol found no difference in the clinical signs or hematological data between FIV-infected and non–FIV-infected cats after infection with either *"Candidatus* M. haemominutum" or *M. haemofelis*.[33a,33b] Further work therefore is required to fully determine the influence of retroviral status on the pathogenicity of hemoplasma infection.

HEMATOLOGICAL FEATURES

Hemoplasma infection typically causes a regenerative anemia. Normoblastemia also may be present,[34] and, as mentioned above, a positive Coombs' test may develop. The nature of hemoplasma anemia often is macrocytic and normochromic,[4,35] although one study found that macrocytosis usually reflected FeLV-positive status.[31] Recent studies following experimental hemoplasma infection at the University of Bristol showed that macrocytic hypochromic anemias develop commonly after *M. haemofelis* infection in FeLV-negative cats.[33a,33b] Interestingly, these same studies failed to demonstrate consistent and significant reticulocytosis in anemic *M. haemofelis* cats, even though their hematocrits increased with antibiotic and/or supportive care. Although reticulocyte counts are problematic in parasitemic cats because of the organisms interfering with the identification of reticulin in erythrocytes, the reason for the lack of significant reticulocytosis in these cats is difficult to explain. Release of sequestered erythrocytes from the spleen could account for an increase in hematocrit without reticulocytosis.

DIAGNOSIS

Blood Smear Examination

The most traditional means of diagnosis of hemoplasma infection is demonstration of organisms on a good quality Romanowsky-stained blood smear (Figure 63-2). Hemoplasmas appear on the surface of the erythrocyte singly, in pairs, or in chains. Acridine orange and direct fluorescent antibody staining methods are reported to be more sensitive than standard Romanowsky stains for demonstrating organisms. However, both of these techniques are limited by the need for a fluorescent microscope. Although some suggest feline hemoplasma species differ in size on cytology,[4] we feel that PCR (see below) is the only reliable means to distinguish between the hemoplasma species. Additionally, cytological diagnosis is known to be associated with both false-positive (e.g., resulting from stain precipitate or Howell-Jolly bodies) and false-negative diagnoses.

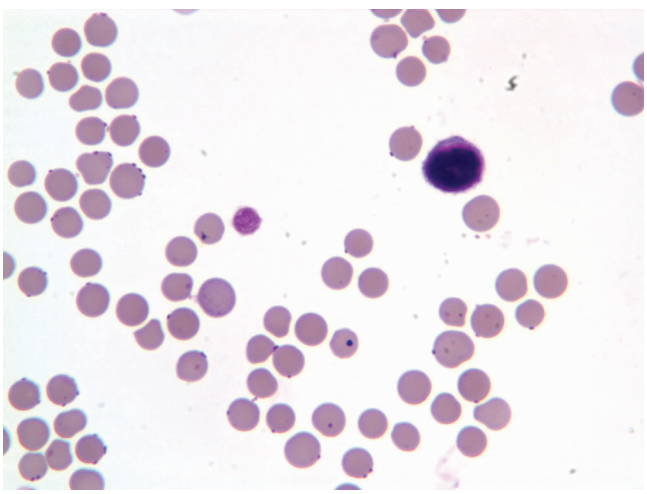

Figure 63-2. Giemsa-stained blood smear from a cat with *M. haemofelis* infection. Note the position of the organisms attached to the surface of the erythrocytes.

Sensitivity is a particular issue with cytology because of fluctuating parasitemia and possible sample handling issues. High concentrations of EDTA anticoagulant dislodge the organism from the erythrocyte cell surface,[10] which makes identification on blood smears extremely difficult. However the concentration of EDTA present in appropriately filled standard blood collection tubes is much lower than that used in the studies showing dislodgement. In studies from the University of Bristol,[14] the EDTA concentration present in standard blood collection tubes was not associated with the specific dislodgement of organisms compared with a standard heparin blood collection tube. The number of organisms attached to the erythrocytes halved after about 12 hours incubation in both EDTA and heparin. However, as a precaution, blood smears should be made within 1 hour of blood collection if cytology is to be used for diagnosis.

Polymerase Chain Reaction

PCR is a technique whereby specific lengths of DNA are amplified so that previously undetectable amounts become detectable. The PCR method has the potential, when designed properly, to be an extremely sensitive and specific test for the diagnosis of feline hemoplasma infection.[36] Commercial laboratories should make available the sensitivity and specificity of PCR assays they offer so that the veterinarian can evaluate their reliability. Additionally, laboratories undertaking PCR should use appropriate negative and positive controls to monitor for contamination or problems with the PCR assay (see Chapter 6).

PCR is more sensitive than blood smear examination in the detection of hemoplasmas,[3,4,15-17,20] and is now considered to be the diagnostic test of choice for feline hemoplasma infection. Conventional nonquantitative PCR assays can detect and distinguish *"Candidatus* M. haemominutum" and *M. haemofelis*.[17] Real-time quantitative PCR assays[20] additionally quantify the amount of hemoplasma DNA present in the patient's blood, which may help determine the significance of the infection. Real-time PCR offers the added advantage of reduced risk of contamination resulting from the ability to measure the PCR without the need to open the PCR tubes, which is a potential source of contamination in conventional PCR. Hemoplasma infection, using the quantitative PCR assay, has been detected as early as 1 day postinfection, and cats remain PCR-positive until antibiotic treatment is started. Cats then can become PCR-negative during antibiotic treatment (however, it may take a number of days or even weeks for the hemoplasma levels to fall to below detection limits) but may become PCR-positive again when antibiotic treatment is stopped.[14] Accordingly, blood samples for hemoplasma PCR should not be collected while a cat is undergoing antibiotic treatment, although a strongly positive result indicates that the therapy is not being

optimally effective. Asymptomatic cats can remain PCR-positive for many months, which indicates the ability of the PCR to detect chronically infected cats.[3,4] Investigators in a recent study found that 10 per cent of healthy cats were infected with feline hemoplasma species,[16] which confirms that a positive PCR result does not always correlate with the presence of clinical hemoplasmal disease.

TREATMENT

Doxycycline is used most commonly to treat hemoplasma infection at a dose of 10 mg/kg/day PO. In our opinion, therapy should be continued for at least 28 days, depending on the response to treatment, which should be assessed clinically and by repeated PCR assays. Reports of the development of esophageal strictures secondary to oral doxycycline treatment have been published[37,38] (see Chapter 10). Therefore oral doxycycline dosing should be followed by the administration of a small amount of syringed water or food to encourage passage of the drug into the stomach. Application of a small amount of butter onto the cat's nose has been shown to be effective in encouraging complete swallowing of orally administered tablets.[39] Short courses (up to 21 days) of doxycycline do not eliminate infection consistently despite being effective for the treatment of anemia.[3,4,40,41] Longer courses of treatment may be required for clearance.[42] Recent studies[40,41] found that 5 and 10 mg/kg/day PO doses of enrofloxacin were associated with clinical improvement in cats inoculated with *M. haemofelis*, but clearance of the organism, as indicated by repeated negative PCR results, did not always result. Diffuse retinal degeneration and acute blindness have been reported after enrofloxacin treatment in cats[43] (see Chapter 31). Although this is said to be a rare and idiosyncratic reaction, doses higher than 5 mg/kg/day, as recommended by manufacturers, should not be used.

Recently attention has been focused on drugs with potent antimycoplasmal activity. However, the macrolide azithromycin, effective for the treatment of several *Mycoplasma*-associated syndromes in human beings, was *not* found to be effective in the treatment of hemoplasmosis in one study.[15] Imidocarb dipropionate, an antiprotozoal agent, has been suggested as a potential treatment for feline hemoplasma infection[44]; however, a recent study found no significant effect of imidocarb on either clinical signs or hematological values resulting from one *M. haemofelis* isolate compared with untreated control cats.[45] Marbofloxacin, in current studies at the University of Bristol, has been shown to reduce *M. haemofelis* organism numbers effectively and treat clinical disease in infected cats at a dose of 2 mg/kg/day PO.[33a,33b] However, consistent elimination of infection (as demonstrated by repeated negative PCR results) was not demonstrated, despite continuing treatment for 28 days. *"Candidatus* M. haemominutum" did not show as favorable a response to marbofloxacin treatment as *M. haemofelis*. Antimicrobial susceptibility differences may exist between *M. haemofelis* and *"Candidatus* M. haemominutum" field isolates. Because neither organism has been cultivated, in vitro antimicrobial susceptibility data are lacking. Future studies should evaluate treatment regimens for each of the specific feline hemoplasma species.

The anemia induced by hemoplasma infection is in part immune-mediated, and corticosteroids have been recommended as adjunct therapy,[46] although their value in treatment is not proven. In our experience, clinically ill cats, including those that are Coombs' positive, respond to antibiotic treatment alone.[14] Supportive care also may be required, including correction of dehydration with fluid therapy. Cats are able to tolerate anemia well; however, if the anemia is severe (hematocrit less than 12 per cent) or if the hematocrit has dropped rapidly, a blood transfusion may become necessary.

PREVENTION

To advise on the prevention of infection is difficult because the epidemiology of hemoplasma infection is poorly understood. Considering the possible methods of transmission of hemoplasma together with the risk factors known, to recommend elimination of blood-sucking arthropods seems prudent, including regular flea control, in addition to a reduction in intercat aggression. Cats that are PCR-positive for hemoplasmas should not be used as blood donors.

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Chapter 64

Tumor-Related Feline Oncology Emergencies

Kelly Chaffin and C. Andrew Novosad

Oncological emergencies may be tumor-related or therapy-related. Tumor-related emergencies can be a result of either the physical presence of the tumor, such as a laryngeal mass causing airway obstruction, or it may be paraneoplastic, such as hypercalcemia. This chapter addresses oncological emergencies with regard to pathophysiology, diagnosis, differential diagnoses, and therapy. Emergencies related to chemotherapeutic toxicities and malignant effusions are presented elsewhere in this section (see Chapters 69 and 67).

SPINAL CORD COMPRESSION

Pathogenesis

Tumors of the central nervous system (CNS) exert their effects by causing a space-occupying lesion that results in compression of the surrounding tissues. Spinal cord compression is the second most frequent neurological complication of metastatic cancer in human beings.[1] Approximately 10 per cent of adult human beings with spinal cord compression present with a known primary tumor or with cord compression as the initial presentation of malignancy.[1] Compression of the spinal cord can be caused by pressure that may be intramedullary, intradural-extramedullary, or extradural. Extradural lymphoma is the most common cause of spinal cord dysfunction in cats.[2] In a study of nonlymphoid vertebral canal tumors in 11 cats, tumor types included meningioma (n = 5), malignant nerve sheath tumors (n = 2), meningeal sarcoma (n = 1), chondrosarcoma (n = 1), lipoma (n = 1), and osteosarcoma (n = 1).[3]

Clinical Signs

Clinical signs associated with neoplastic spinal cord compression may vary depending on the size and location of the tumor. Cats may exhibit sensory loss, pain, weakness, ataxia, and paralysis.[4] In one study of 21 cats with spinal lymphoma, 81 per cent had hind limb paresis and results of feline leukemia virus (FeLV) testing were positive in 84 per cent of cats.[2] Asymmetrical paraparesis, focal hyperesthesia, and rapidly progressive ataxia were the most common clinical signs in another study of 23 cats with spinal lymphoma.[5] Spinal lymphoma is a disease of young cats with a reported median age of approximately 24 months.[5]

Diagnosis

A thorough neurological examination is imperative to localize the lesion. A complete blood cell count, biochemical profile, urinalysis, and FeLV and feline immunodeficiency virus (FIV) status should be evaluated in any cat with acute onset of hind limb paresis. A bone marrow aspirate may be beneficial in establishing the diagnosis of spinal lymphoma, because in one study, 68.7 per cent of cats with spinal lymphoma had leukemic bone marrows.[2] Survey radiographs of the spine may reveal bone lysis, fractures, collapse of an intervertebral disc space, or an adjacent soft tissue mass (Figure 64-1). Advanced imaging techniques, such as myelography, computed tomography (CT), or magnetic resonance imaging (MRI), often are necessary for localization of the compressive lesion (Figures 64-2

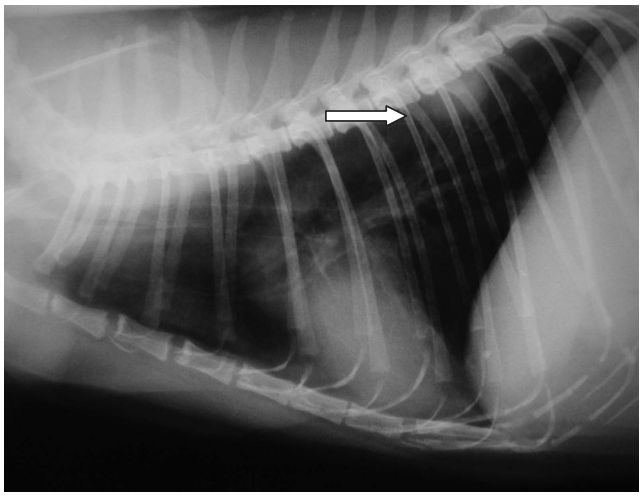

Figure 64-1. Thoracic radiograph from a cat that presented with an acute onset of hindlimb paresis/paralysis. The arrow demonstrates a soft tissue mass associated with T8-T9. The mass was aspirated and was consistent with a plasma cell tumor.

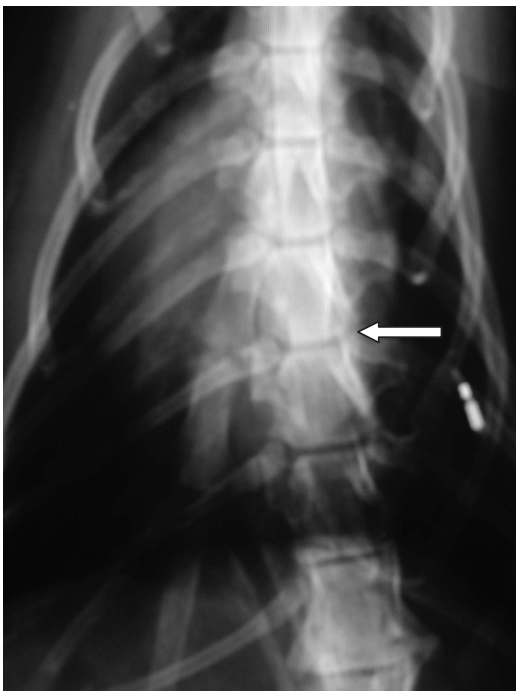

Figure 64-2. Myelogram of the same cat in Figure 64-1 demonstrating a compressive lesion *(arrow)* of the spinal cord.

and 64-3). Cerebrospinal fluid (CSF) analysis also should be evaluated, because malignant lymphocytes diagnostic for lymphoma have been identified in approximately 35 per cent of cats with spinal lymphoma.[5]

Treatment

The diagnosis and subsequent treatment of spinal cord compression must be undertaken early, especially if neurological signs are acute and progressive. Surgical decompression of the spinal cord and debulking of the tumor may not only yield a definitive diagnosis but also may result in temporary improvement in neurological function.[6] Decompressive surgery can

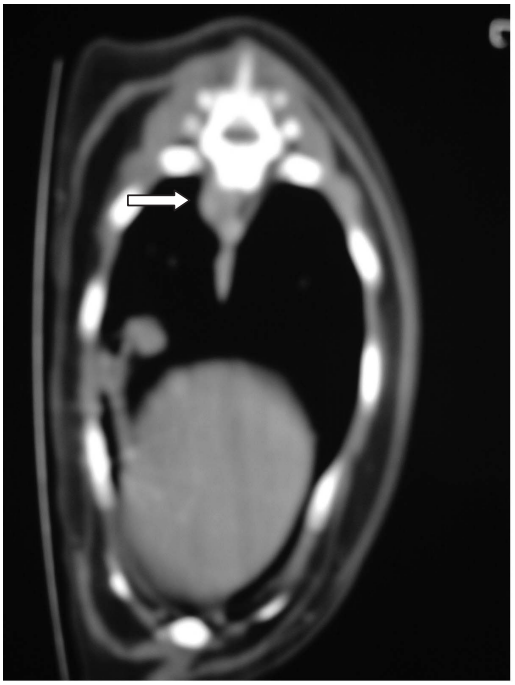

Figure 64-3. CT scan of the same cat in Figures 64-1 and 64-2 at the level of T8-T9 illustrating the soft tissue mass *(arrow)* present at the ventral aspect of the thoracic vertebrae. The cat was staged clinically for multiple myeloma and was negative. Systemic chemotherapy was initiated and neurological function improved in a matter of days from the initiation of therapy.

result in improved survival in cats with nonlymphoid vertebral tumors.[3] Radiation therapy is the preferred treatment for spinal tumors that cannot be resected surgically. Cats with spinal lymphoma should be treated with systemic chemotherapy used alone or in combination with surgical debulking and radiation therapy.[5] Chemotherapy is considered the initial treatment of choice for spinal lymphoma because most cats have multicentric disease.[2] The complete remission rate was 50 per cent in six cats treated with cyclophosphamide, vincristine, and prednisone with a median duration of 14 weeks.[2] Complete remissions were not observed in three cats treated with corticosteroids alone.[2] Chemotherapy combined with radiation therapy or surgery resulted in improvement in three cats in one series, but only one cat had long-term improvement (13 months).[5]

SEIZURES

Pathogenesis

A seizure is an episode of abnormal brain activity characterized by a sudden, uncontrolled discharge from neurons of the brain. Seizures can be caused by numerous diseases, including intracranial and extracranial processes (see Chapter 55).[7,8] These causes include such intracranial disorders as primary brain tumors (meningiomas, astrocytomas, oligodendrogliomas) and metastatic tumors (adenocarcinomas, hemangiosarcomas).[8] Other intracranial causes include infectious diseases (feline infectious peritonitis, rabies, FeLV, toxoplasmosis, cryptococcosis) and vascular anomalies.[7,8] Extracranial causes of seizures include metabolic disorders (hepatic encephalopathy, uremia, electrolyte disturbances, polycythemia), nutritional deficiencies (thiamine), and toxins.[7,8]

Seizures also have been reported in cats after the use of several chemotherapy drugs including mitoxantrone, 5-fluorouracil (5-FU), and chlorambucil.[9,10]

Clinical Signs

Seizures can be classified into two categories based on their clinical presentation. Generalized seizures often present with loss of consciousness and involuntary motor activity that involves tonic or clonic muscle contractions, limb paddling, and vocalizing.[7,8] Partial seizures may be focal or complex in nature.[7] Simple partial seizures do not impair consciousness, whereas, in complex partial seizures, consciousness is either impaired or lost completely.[7] Simple partial seizures may present with such signs as facial twitching, involuntary motor movements, and abnormal head movements.[7] Complex partial seizures often are characterized by abnormal behavior or circling.[7] In a recent retrospective study of 160 cats with intracranial neoplasia, the most common neurological signs were altered consciousness (26 per cent), circling (22.5 per cent), and seizures (22.5 per cent).[11]

Diagnosis

The diagnosis of seizures involves a combination of historical information and signs at presentation. If a patient presents in status epilepticus, emergency treatment to control the seizures should be instituted before a complete diagnostic evaluation. Important information to obtain from owners includes level of consciousness, current medications, involuntary motor activity, urination, and defecation.[8] In addition to a thorough neurological examination, bloodwork including a complete blood cell count, biochemistry profile, thyroid hormone levels, and FeLV and FIV tests should be obtained. Serial neurological examinations should be performed to determine whether neurological deficits are repeatable or whether they are transient and related to the postictal period. A complete ophthalmological examination also is indicated to search for evidence of inflammation or retinal hemorrhage secondary to hypertension. A blood pressure measurement should be evaluated in all cats with seizures to rule out hypertension as an underlying cause. After stabilization of the patient, additional diagnostic tests such as MRI, CT, and CSF analysis often are necessary for diagnosis of intracranial disease (Figures 64-4 and 64-5).

Treatment

If a cat is presented having a seizure, an intravenous catheter should be placed and diazepam should be administered at a dose of 0.5 to 1.0 mg/kg IV.[7,8,12] This dose can be repeated up to three times per hour, but the patient should be monitored for sedation and respiratory depression.[12] Maintenance phenobarbital at a dose of 2 mg/kg IV or IM can be administered every 6 to 8 hours if diazepam is inadequate for seizure control.[12] The reader is referred to Chapter 55 for a detailed discussion of the causes and management of seizures.

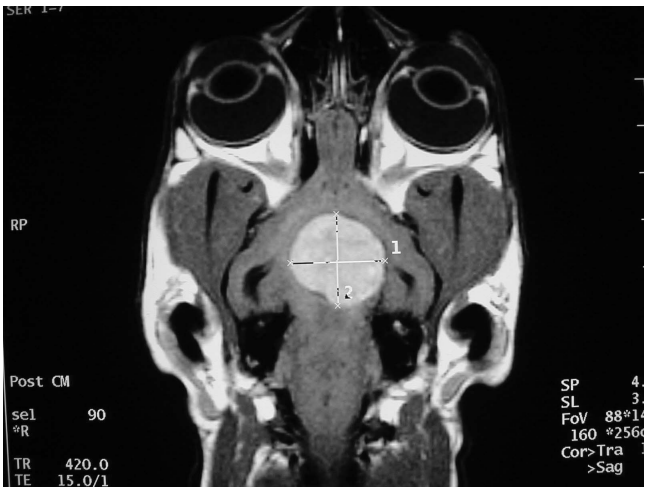

Figure 64-4. MRI from a cat that presented with acute onset of generalized seizures. An MRI is extremely helpful to determine the location of masses in the brain and appropriate therapy.

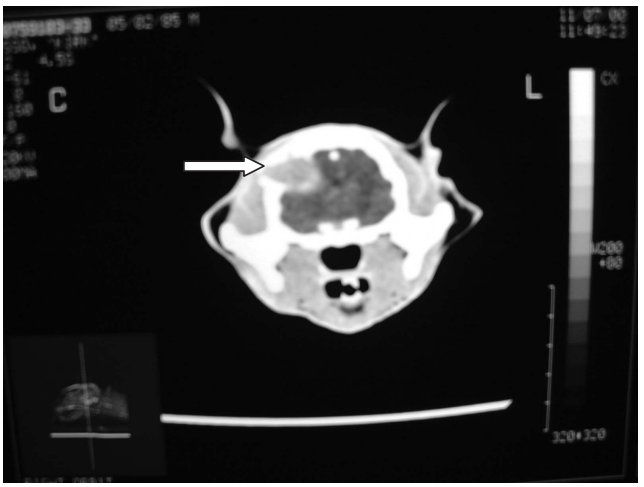

Figure 64-5. CT image of a brain tumor from a cat with seizures. Note the peripheral location of the mass *(arrow)* and contrast enhancement exhibited by the mass. This cat was treated with surgery and the diagnosis was a meningioma.

HYPERVISCOSITY SYNDROME

Pathogenesis

Hyperviscosity syndrome (HVS) refers to a collection of clinical signs resulting from increased serum or whole blood viscosity. Serum viscosity is determined by the concentration, size, and shape of serum proteins.[13] In human beings, hyperviscosity is observed most often in Waldenstrom's macroglobulinemia with IgM, followed by IgA myeloma, and is least common in IgG myeloma.[14] The most common cause of monoclonal hyperglobulinemia in cats is multiple myeloma (see Chapter 62).[15-17] HVS also has been reported to occur secondary to lymphoma and an extramedullary plasmacytoma in cats.[18,19] In contrast to human beings, IgG is the immunoglobulin responsible most often for multiple myeloma and HVS in cats.[15-17]

Clinical Signs

HVS usually manifests with circulatory problems secondary to sludging of blood leading to inadequate perfusion. Common organ systems affected by HVS include CNS, renal, cardiovascular, and ophthalmic. Coagulation abnormalities also are common, and signs associated with coagulopathies often are

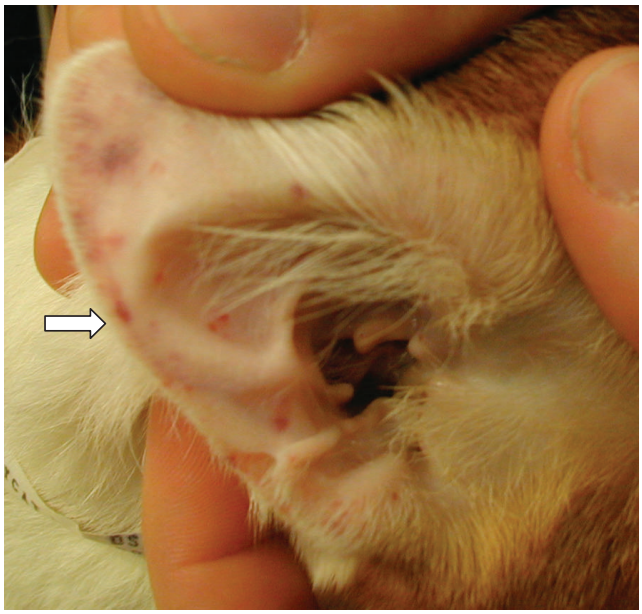

Figure 64-6. Notice the petechial and ecchymotic hemorrhages *(arrow)* present on the pinna of the right ear of a cat. This cat was originally presented for anorexia and lethargy when the coagulation abnormalities were noted.

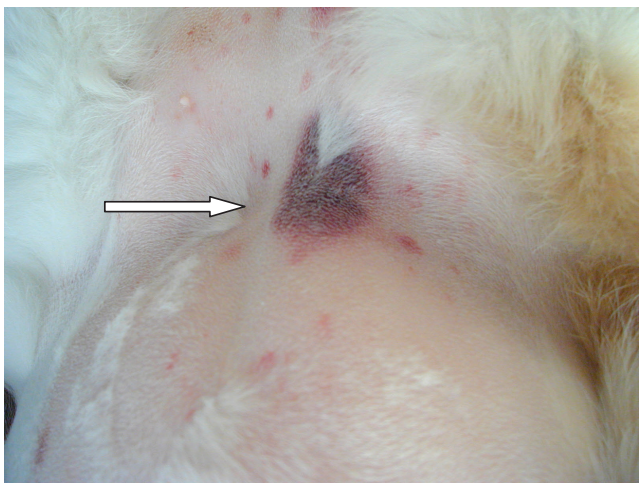

Figure 64-7. The same cat as in Figure 64-6. Note the large bruise and ecchymotic hemorrhages *(arrow)* present on the ventral thorax. This cat was diagnosed with multiple myeloma with secondary hyperviscosity syndrome (HVS).

secondary to platelet dysfunction including mucosal hemorrhage, melena, and ecchymoses (Figures 64-6 and 64-7). In one report of two cats with multiple myeloma and HVS, clinical signs included pale mucous membranes, dehydration, retinal hemorrhages, dilated and tortuous retinal vessels (see Figure 62-1), seizures, head-tilt, nystagmus, systolic murmur, and a gallop rhythm.[15]

Diagnosis

The diagnosis of HVS should be suspected in any cat with hyperglobulinemia and clinical signs related to the organ systems listed above. Patients with hyperglobulinemia should have a minimum database performed including a complete blood cell count, biochemistry panel, and urinalysis. A serum electrophoresis is recommended to confirm the presence of a monoclonal gammopathy (see Figure 62-2). The urine also should be screened for Bence-Jones proteins with a heat precipitation test. The serum viscosity can be determined using an Ostwald viscosimeter. Normal values for cats have been reported in two separate studies to be less than 2.5 and less than 1.7.[16,18] A bone marrow aspirate also should be considered if a monoclonal gammopathy is present to aid in diagnosing multiple myeloma or lymphoma.

Treatment

The treatment of HVS involves treatment of the underlying disease and reduction of the serum viscosity. Chemotherapy is indicated to reduce the tumor volume in multiple myeloma and lymphoma. Plasmapheresis can be used to reduce the protein concentration but is not widely available in veterinary medicine.[21] In the absence of the specialized equipment required for plasmapheresis, whole blood can be removed from the patient and separated into plasma and cells. The plasma subsequently is discarded and the cells are suspended in an equal volume of 0.9 per cent NaCl and administered intravenously to the patient.[21] If dehydration or renal impairment is present, appropriate fluid diuresis may be beneficial. Patients with HVS also should be screened carefully for infection secondary to immunosuppression and treated appropriately with bactericidal antibiotics (see Chapter 69).

PATHOLOGICAL FRACTURE

Pathogenesis

Bone fractures occur by several mechanisms, including traumatic and pathological. Traumatic fractures are secondary to excessive force being applied on normal bone, which leads ultimately to the break. In the case of pathological fractures, the bone is abnormal and breaks with minimal trauma or normal weightbearing.[22] Any type of pathology that weakens the bone may predispose the bone to fracture, especially neoplasia. Tumors affecting bone may be primary tumors that arise in bone or cartilage (osteosarcoma, chondrosarcoma, fibrosarcoma, synovial sarcoma) or metastatic tumors (adenocarcinoma, hemangiosarcoma). In human beings, bone is the third most common site of distant metastasis, with only lung and liver being more common.[23] One other important malignancy that can cause bone destruction is multiple myeloma. Plasma cell infiltration of bone can cause osteolysis and may predispose to pathological fractures (Figure 64-8).[24,25]

Clinical Signs

Lameness is the most common presenting complaint with pathological fractures in the appendicular skeleton. In one report of osteosarcoma in 22 cats, lameness was a clinical finding in all 15 cats with appendicular tumors.[26] Two cats in that study presented with an acute onset of lameness and both had pathological fractures at the time of diagnosis.[26]

Diagnosis

The diagnosis of a pathological fracture of the appendicular skeleton is best demonstrated through radiographs of the

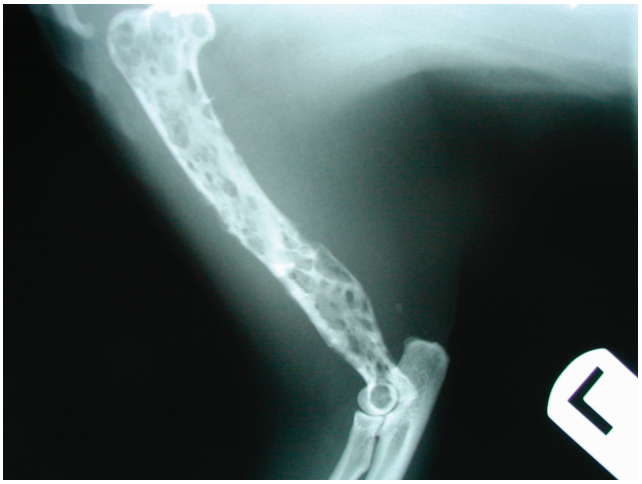

Figure 64-8. Radiograph of a cat with multiple myeloma. Note the extensive lytic bone lesions present throughout the humerus.

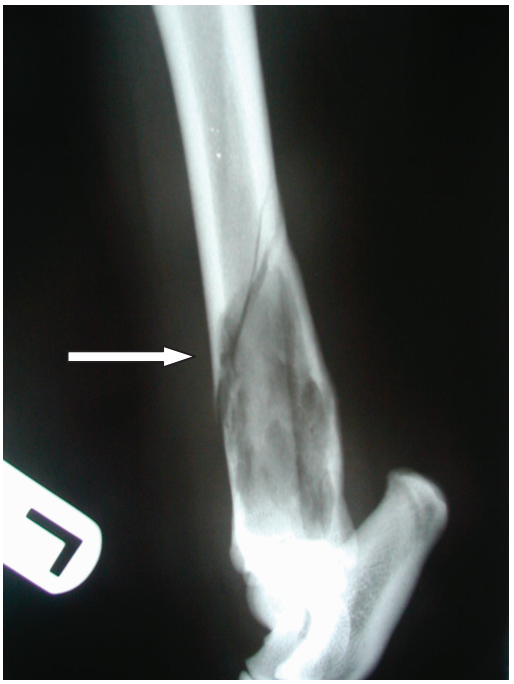

Figure 64-9. Radiograph of the tibia of a cat that presented with a pathological fracture *(arrow)* of the distal tibia. An amputation was performed and the diagnosis of an appendicular osteosarcoma was made.

affected bone (Figure 64-9). In addition to radiographs of the affected region, laboratory evaluation including a complete blood cell count, biochemistry, and urinalysis should be evaluated to search for underlying disease processes. Additional imaging (thoracic radiographs, abdominal radiographs, abdominal ultrasound) is indicated in any patient with a suspected pathological fracture to rule out distant metastatic disease. If hyperglobulinemia is present, additional staging for multiple myeloma, as described in the section on HVS, is recommended.

Treatment

Regardless of the etiology of the pathological fracture, immediate treatment should center on stabilization of the fracture and pain management. Amputation of the affected limb is indicated for osteosarcoma, as long as no evidence exists of distant metastatic lesions. Surgical stabilization of pathological fractures has been reported in dogs with multiple myeloma, but no studies in cats have been reported.[27] Palliative radiation therapy also can be used as an option to reduce pain and improve quality of life.[28]

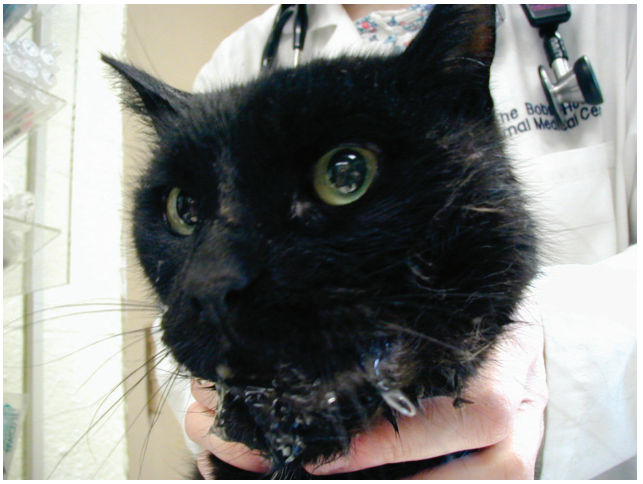

Figure 64-10. This cat presented for evaluation of mandibular swelling and dysphagia. Note the ptyalism associated with the mandibular mass.

DYSPHAGIA

Pathogenesis

Dysphagia refers to the inability to swallow or difficulty related to the act of swallowing. Dysphagia can result from obstructive or functional abnormalities of the oral cavity, pharynx, or esophagus. Squamous cell carcinoma (SCC) is the most common oral tumor in cats.[29] In human beings, risk factors associated with the development of oral malignancies include tobacco exposure, diet, poor dental hygiene, and infectious diseases (herpes simplex virus type 1, syphilis).[30] The etiology of feline oral SCC is unknown, but a recent report suggests that exposure to flea control products, diet, and environmental tobacco smoke may be risk factors, although further investigation is needed.[31] This discussion focuses on tumors of the oral cavity and the subsequent dysfunction they may cause, which prompts immediate intervention for nutritional support.

Clinical Signs

The most common presenting complaint in cats with oral SCCs is a mass or facial asymmetry noted by the owner or veterinarian (Figure 64-10).[32] Other common signs include ptyalism, anorexia, loose teeth, dysphagia, weight loss, and halitosis.[32] Oral SCCs have been reported involving the tonsil, pharynx, maxilla, mandible, but the most common site is the sublingual area.[32-34]

Diagnosis

The diagnosis of an oral tumor involves histological assessment of the mass. Before a biopsy is procured, routine laboratory evaluation including a complete blood cell count, biochemistry,

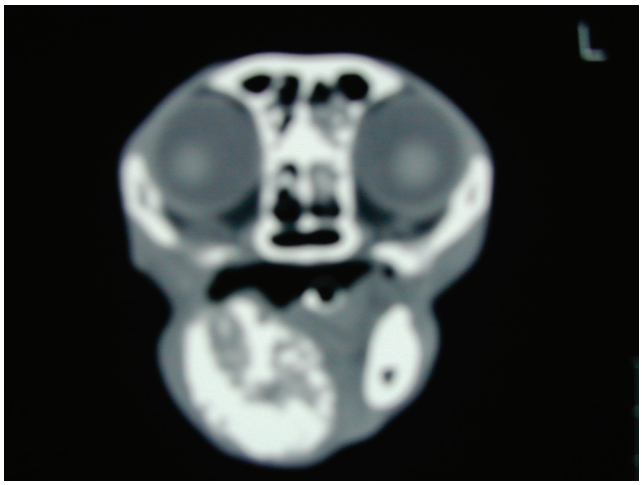

Figure 64-11. CT image from the cat in Figure 64-10. This mass was biopsied and the diagnosis was an oral squamous cell carcinoma.

and urinalysis should be performed. Thoracic radiographs and lymph node aspirates to assess for metastatic pulmonary or lymphoid disease also are indicated before a biopsy is obtained. Imaging of the oral cavity also may be helpful to determine the extent of bone involvement. Routine skull radiographs or dental radiographs are effective at demonstrating bone involvement if present. Advanced imaging techniques, such as CT and MRI, are becoming widely available and offer the advantage of defining the tumor volume (Figure 64-11).

Treatment

Regardless of the type of oral malignancy causing dysphagia, particular attention should be given to the nutritional state of these patients. Cats with oral tumors often have functioning gastrointestinal tracts, but the mass prevents swallowing by obstruction or pain. The placement of a feeding tube allows proper nutrition to be provided regardless of the type of treatment decisions that are made for the patient. A recent study compared the complication rates between esophagostomy and percutaneous endoscopic gastrostomy feeding tubes and found no difference.[35] Both types of tubes were well tolerated and allowed for long-term enteral feeding for cats (see Chapter 16). In addition to proper nutrition, analgesics and antibiotic therapy may help to improve quality of life.

HYPERCALCEMIA

Etiology and Pathogenesis

Calcium is a second messenger required for many cellular biochemical functions including blood coagulation, muscle contraction, muscle tone, membrane stability, bone formation, liver function, cell cycle functions, and nerve conduction.[36] Normal serum calcium is maintained by close regulation of intestinal calcium absorption, renal calcium absorption, and turnover of skeletal calcium through the combined effects of parathyroid hormone (PTH) and cholecalciferol (vitamin D_3).[37]

In cats, hypercalcemia is defined as fasting serum total calcium greater than 11.0 mg/dL or ionized calcium greater than 1.4 mmol/L (see Chapter 17).[38,39] In dogs, total calcium levels often are corrected by calculation to adjust for extensive binding to albumin. Similar calculated adjustments are not valid in cats.[40]

Humoral hypercalcemia of malignancy (HHM) is a common cause of persistent pathological hypercalcemia in cats.[41] The principal source of calcium in HHM is osteoclastic bone resorption, although increased renal tubular resorption and intestinal absorption also can contribute. The majority of cases result from the production of humoral factors by tumor cells that stimulate bone resorption at sites distant from the primary tumor. These humoral factors include PTH, a PTH-related peptide (PTH-rp), 1,25-dihydroxyvitamin D, prostaglandins, osteoclast activating factors, transforming growth factors, and a series of cytokines (IL-1, IL-4, IL-6, TNF-α, and TNF-β), also called osteoclast-activating factors.[36,37] Cytokine-mediated direct stimulation of bone resorption adjacent to bone metastases is a less common mechanism of HHM.[37]

Recent validation of an assay to measure PTH-rp in cats demonstrates that PTH-rp is a cause of HHM in cats.[39] PTH-rp binds to the N-terminus of PTH receptors in bone and kidneys, and through mimicking the action of PTH, causes bone resorption and increased renal reabsorption of calcium.[42] The most common cause of HHM is synthesis of PTH-rp by tumor cells. Cytokines cause hypercalcemia by several different mechanisms including their synergistic/additive properties to the actions of PTH-rp on osteoclast function, and through induction of local bone resorption by hematopoietic neoplasia such as multiple myeloma or metastatic carcinoma.[36]

Pathophysiology and Clinical Signs

Prolonged hypercalcemia can affect many organ systems adversely. Mechanisms for development of these clinical signs are related to the function of calcium as a messenger necessary for multiple cellular functions. Clinical signs can vary greatly from patient to patient, from the asymptomatic patient diagnosed incidentally on routine biochemistry screening to the patient experiencing dysfunction or even failure of multiple organ systems.[37]

Abnormal renal function accompanies hypercalcemia frequently as a result of functional and structural renal changes. The functional effects usually are reversible, but the structural changes may be permanent. Defective urine concentrating ability and the clinical signs of polyuria develop as a result of acquired, but reversible, inability of renal tubular cells and collecting ducts to respond to antidiuretic hormone (ADH), and secondary reduction in cyclic adenosine monophosphate (cAMP). These changes contribute to the development of compensatory polydipsia. Basement membrane, tubular, interstitial, and even mitochondrial, renal tissue mineralization are structural changes that may occur and contribute to impaired concentrating ability and progression to renal cell death.[36] Azotemia results from a combination of prerenal and renal factors. Vomiting and polyuria cause volume contraction and the development of prerenal azotemia. Renal azotemia results from hypercalcemia-induced renal vasoconstriction and decreased glomerular filtration rate. Sustained renal vasoconstriction and progressive nephrocalcinosis may lead to ischemic tubular injury promoting the development of structural changes that further worsen renal function. Sustained hypercalcemia ultimately can lead to irreversible kidney damage.[36,37]

Hypercalcemia also has adverse effects on other body tissues including the peripheral and central nervous systems

and all muscle tissues, including skeletal, smooth, and cardiac. Decreased cell membrane permeability and excitability in nervous and muscle tissue can result in listlessness, depression, weakness, inappetence, and decreased activity. Involuntary movements such as twitching, shivering, and even seizures are a result of possible cerebral microthrombi, cerebral vasospasm, and interference with protective mechanisms within the brain to prevent seizures.[36]

The effects of hypercalcemia on gastrointestinal smooth muscle, parietal cells, and the pancreas can result in inappetence, vomiting, constipation, gastroduodenal ulceration, and pancreatitis.[37] Calcium is an important regulator of the excitation-contraction coupling of heart and of smooth muscle tone in peripheral vessels. Cardiac arrhythmias can develop from direct effects of calcium resulting from rapid mineralization of cardiac tissue and elevated catecholamine levels. Hypertension is recognized in human beings but has not been recognized in small animal patients.[37]

Associated clinical signs that may be seen in cases of hypercalcemia are listed in Table 64-1.[36]

Differential Diagnoses

The most common differential diagnoses of hypercalcemia in cats are HHM, primary hyperparathyroidism, and chronic kidney disease (see Chapter 17). Other reported causes that are less common include granulomatous disease,[43] vitamin D intoxication, rodenticide ingestion or plant ingestion (*Cestrus diurnum* [day-blooming jessamine]; *Solanum malacoxylon*, and *Trisetum flavescens*),[37] and hypoadrenocorticism.[44,45] Interestingly, a significant number of cats have been diagnosed with mild to moderate hypercalcemia for which no underlying cause apparently exists and subsequently is called idiopathic hypercalcemia.[41,46]

Hypercalcemia of malignancy in cats has been reported with lymphoma, multiple myeloma, SCC, undifferentiated carcinoma, thyroid carcinoma, parathyroid adenoma/adenocarcinoma, bronchogenic carcinoma, myeloproliferative disease, myelosiderosis, erythroleukemia, aleukemic leukemia, osteosarcoma, fibrosarcoma, and lymphocytic leukemia.[39,41,47-51]

Laboratory error also is a common cause of hypercalcemia. In patients without clinical or physical examination findings consistent with hypercalcemia, repeated blood sampling for re-evaluation of calcium levels is recommended.[36,38]

Table 64-1 | **Clinical Signs of Hypercalcemia**

GASTROINTESTINAL
Anorexia
Vomiting
Constipation
URINARY
Polyuria
Polydipsia
Dysuria
CENTRAL NERVOUS SYSTEM
Mental dullness
Obtundation
Coma
Seizure
MUSCULOSKELETAL
Stiff gait
Shivering
Muscle wasting
Weakness
Exercise intolerance
Pain/lameness
NONSPECIFIC
Weight loss
Lethargy

Diagnosis of Hypercalcemia

A thorough physical examination including peripheral lymph node palpation, oral examination, mammary chain palpation, thyroid (ventral cervical) palpation, abdominal palpation, and skeletal palpation is likely to provide valuable information to help determine the cause of hypercalcemia.

Laboratory evaluations that should be performed in all hypercalcemic cats include complete blood count, serum biochemistry profile, and complete urinalysis. Ionized calcium values may be helpful to differentiate renal hypercalcemia from other causes of hypercalcemia. Hypercalcemia of malignancy most often is associated with increased ionized calcium, whereas ionized calcium typically is normal or decreased in cases of chronic kidney disease.[42]

PTH levels and PTH-rp levels as determined by immunoassay can be valuable in determination of the cause of hypercalcemia. These assays have been validated recently for use in cats and should be evaluated in concert with ionized calcium.[39] Increased PTH-rp has been reported in animals with chronic kidney disease and no evidence of malignancy.[36]

Thoracic radiography, abdominal radiography, and abdominal sonography may be helpful in detecting masses (mediastinal masses, lymphadenopathy, pulmonary metastases, splenomegaly, hepatomegaly, abdominal masses, or osteolytic skeletal lesions).

Treatment

Numerous factors must be considered in determination of the appropriate course of therapy for hypercalcemia. Factors including magnitude of hypercalcemia, rate of development, clinical status of patient (degree of neurological, cardiac, and renal dysfunction), and other electrolyte (phosphorus, potassium, magnesium) imbalances should be considered. Treatment should be aimed at reducing serum calcium levels. This may be accomplished by increasing urinary excretion of calcium, inhibiting bone resorption of calcium, and blocking intestinal absorption of calcium. Definitive treatment of hypercalcemia lies in the determination and treatment of the underlying cause.[37]

Intravenous fluid therapy is employed commonly in management of the hypercalcemic patient. Isotonic saline solution (0.9 per cent NaCl) is the fluid of choice. Calciuresis is promoted by expansion of extracellular volume and increased glomerular filtration rate. The rate of fluid administration should be based on determination of the patient's volume status (estimate of dehydration), renal function, cardiac function, maintenance needs (40 to 60 ml/kg/day), and ongoing losses. Careful monitoring of urine output, body weight, respiratory rate, and heart rate is important in all patients, but particular attention should be given to those cats with known or suspected

renal or cardiac dysfunction.[36] Monitoring of central venous pressure is recommended in critical patients.[52] Other electrolytes (potassium, phosphorus, and magnesium) may need to be supplemented in these patients. Intravenous potassium administration should not exceed 0.5 mEq/kg/hr.

In some patients, volume expansion alone may be enough to reduce serum calcium sufficiently until definitive therapy for the underlying cause can be initiated. If additional therapy is needed, diuretics or glucocorticoids often are the first therapies employed. Other therapies to be considered, but rarely employed, include biphosphonates, calcitonin, and mithramycin.

Furosemide (2 to 4 mg/kg PO, SQ, or IV q8-12h) interferes with renal calcium reabsorption. This effect is related directly to the amount of sodium delivered to the kidney, which makes volume expansion with saline before treating with diuretics essential. Thiazide diuretics should never be used because they enhance calcium reabsorption in the distal tubule and may exacerbate hypercalcemia.[36,37,51]

Glucocorticoids (prednisone 1.0 to 2.2 mg/kg PO, SQ, or IV q12h or dexamethasone 0.1 to 0.22 mg/kg SQ or IV q12-24h)[49] reduce calcium by inhibiting osteoclast bone resorption and by inhibiting vitamin D–mediated intestinal absorption of calcium while increasing renal excretion of calcium.[37] Because glucocorticoids may cause rapid reduction of tumor volume in cases of lymphoma, they should be withheld until the diagnosis is confirmed.

Biphosphonates (etidronate 5 to 20 mg/kg/day SQ q12h)[53] inhibit osteoclastic bone resorption, retard deposition of hydroxyapatite in bone collagen, increase unmineralized osteoid, and inhibit formation of calcium phosphate crystals.[36,37] Salmon calcitonin (4 to 6 IU/kg IM q12h) inhibits osteoclastic bone resorption and increases renal calcium excretion. Other benefits of calcitonin include analgesic properties, rapidity of action, and low risk of toxicity (anorexia, vomiting, and diarrhea). Disadvantages of calcitonin use include cost, unpredictability of action, and drug resistance. Resistance can be delayed with co-administration of glucocorticoids or discontinuation for 24 to 48 hours.[37]

Plicamycin (mithramycin 25 µg/kg IV in dextrose 5 per cent in water over 2 to 4 hours) can be given as often as one to two times weekly. This drug inhibits osteoclastic bone resorption and decreases bone turnover. Response typically is seen within 24 to 48 hours of administration, and effects may last 3 to 7 days. The toxicity profile includes anorexia, vomiting, thrombocytopenia, hepatotoxicity, and nephrotoxicity.[37]

HYPOGLYCEMIA

Etiology

Maintenance of a euglycemic state requires a constant balance of biochemical processes (gluconeogenesis, glycogenolysis, glycogen synthesis) and the availability of gluconeogenic substrates (amino acids, fatty acids, and glycerol) mediated by the interaction of hormones (insulin, glucagon, cortisol, and growth hormone) and the autonomic nervous system (epinephrine, norepinephrine). Hypoglycemia can develop with dysregulation of any one of these homeostatic mechanisms. Hypoglycemia may result from increased glucose utilization, decreased glucose production, deficiency in diabetogenic hormones, inadequate diet of glucose precursors, or some combination of these mechanisms.[54,55] Hypoglycemia is defined as a blood glucose concentration less than 60 mg/dL.[54] Blood glucose concentrations of less than 40 mg/dl may result in seizure, coma, or death.[56]

Insulin-producing islet cell tumors and non–islet cell tumors may cause hypoglycemia. Insulin-producing islet cell tumors cause hypoglycemia by unregulated production of insulin. Non–islet cell tumors may cause hypoglycemia through one of several proposed mechanisms, including increased glucose utilization by tumors of large volumes; decreased liver function (diminished gluconeogenesis, glycogenolysis, or glycogen synthesis); production of insulin-like polypeptides such as polypeptide growth factors including insulin-like growth factor I and II (IGFI and IGFII), somatomedin A, and somatomedin C; and failure of counterregulatory mechanisms such as depression of counterregulatory hormones, for example, glucagon, adrenocorticotrophic hormone, glucocorticoids, and growth hormone. Peripherally, upregulation of insulin receptors also is proposed to be a cause of hypoglycemia.[57,58]

Pathophysiology

Hypoglycemia affects the nervous system most dramatically. Glucose is the most important energy substrate for the brain. Glucose metabolism and oxygen consumption in the brain are closely linked. With decrements in blood glucose are commensurate reductions in cerebral oxygen consumption. Within the brain are regional differences in glucose metabolism and therefore differing susceptibilities to the adverse effects of hypoglycemia.[59] As the brain is deprived of glucose, rostral-to-caudal progression of signs occurs because higher brain centers are more sensitive to the insult.[60]

The risk of prolonged or permanent neurological injury is related to the severity and duration of the hypoglycemia. In situations of severe, prolonged hypoglycemia, neurological deficits may persist for days or weeks despite correction of hypoglycemia. Hypoglycemia causes cortical lesions, especially in the temporal lobes, and injures middle layers of the cerebral cortex and hippocampus while sparing the brain stem and spinal cord. Chronic, recurrent hypoglycemia may result in a predominantly motor-sensorimotor peripheral neuropathy.[59] Prolonged hypoglycemia can cause focal necrosis of the cerebral cortex, resulting in an acquired seizure disorder.[61] Irreversible lesions may result from long-term severe hypoglycemia and the subsequent hypoxia, which predisposes to the development of cerebral edema.[62]

Clinical Signs

Clinical signs of hypoglycemia are attributable to neuroglycopenia and activation of the autonomic nervous system.[59] Clinical signs caused by increased sympathetic tone are the adrenergic signs of mydriasis, tachycardia, tremors, irritability, nervousness, and vocalization.[60] Clinical signs caused by neuroglycopenia develop initially in higher brain centers, with cortical signs such as dullness, confusion, and seizures being most common. Progression to include lower brain areas results in signs such as bradycardia, hypothermia, miosis, and decerebrate rigidity. Vestibular signs such as nystagmus also may be present. As clinical signs progress, tendon reflexes are lost as motor neurons are affected.

Differential Diagnoses

Artifactual changes in blood glucose are an important differential diagnosis for hypoglycemia. Serum or plasma must be separated from cellular components of blood within 30 minutes after collection to minimize consumption of glucose by cells. At 22° C, the glucose concentration decreases approximately 10 per cent every 30 to 60 minutes. Glucose concentration may decrease more rapidly in the presence of large concentrations of metabolically active cells as with leukocytosis or leukemia.[38]

In cats, pathological causes of hypoglycemia include neoplasia, sepsis, pathological increases in blood cells (polycythemia or leukemia), and liver failure.[60] Insulin-producing islet cell tumors (insulinomas) and lymphoma have been reported to cause hypoglycemia in cats.[47,63] Non–islet cell tumors that have been reported to result in hypoglycemia in other species include fibrosarcoma, leiomyoma, rhabdomyosarcoma, liposarcoma, mesothelioma, hepatoma, hepatocellular carcinoma, hemangiosarcoma, oral malignant melanoma, plasma cell tumor, multiple lymphoma, and salivary gland tumors.[57,58]

Diagnosing the Cause of Hypoglycemia

Hypoglycemia can be diagnosed reliably with an in-house glucometer, or by standard laboratory methods through a commercial laboratory. In the emergency setting, a readily accessible glucose monitor is advantageous.

A number of diagnostic tests should be evaluated to determine the cause of hypoglycemia. Routine complete blood count, serum chemistries, and urinalysis can be used to assess the overall health status of the cat and to investigate potential causes of hypoglycemia, including liver disease, increased blood cell counts, and sepsis. If sepsis is strongly suspected, urine and blood cultures also should be considered. Thoracic and abdominal radiography and abdominal sonography can be used to screen for neoplasia. Insulinomas are detected uncommonly by these techniques. However, these diagnostic tests can be important to rule out other tumor types and to avoid surgery in those patients with grossly detectable, widespread metastases. Abdominal sonography also may demonstrate evidence of metastatic beta cell tumors in the liver or regional abdominal lymph nodes.

Confirmation of insulin-secreting neoplasia requires documentation of inappropriate insulin secretion despite hypoglycemia. Serum insulin and glucose levels should be evaluated concurrently. If the blood glucose concentration is less than 60 mg/dL and the serum insulin concentration is increased (i.e., more than 20 µU/mL) or in the high normal range (i.e., 10 to 20 µU/mL), the presence of an insulin-secreting neoplasm is likely.[38]

The amended insulin glucose ratio has been recommended to investigate the relationship of insulin to glucose.[63,65] The formula for calculation of the amended insulin glucose ratio is extrapolated from the human literature, and assumptions made by the formula may not be directly applicable to veterinary species. The amended insulin glucose ratio has been found to have a higher percentage of false-positive results than comparison of absolute serum insulin to glucose during hypoglycemia,[64] so use of this ratio is not recommended to diagnose insulin-secreting tumors.[55,62] Current diagnostic recommendations include evaluating the history, physical examination findings, clinicopathological data, abdominal sonography, and comparison of absolute serum insulin and glucose during an episode of hypoglycemia.[55,62,64]

Provocative testing (glucose tolerance test, glucagon tolerance test, and tolbutamide tolerance testing) has not proven to be more reliable that the amended insulin glucose ratio[65] and is not recommended.[55] With advancement in nuclear diagnostic techniques, nuclear scintigraphy using radiolabeled octreotide may become available at veterinary diagnostic centers in the future. Octreoscan scintigraphy is reported to have 75 to 86 per cent sensitivity in diagnosing beta cell tumors in human beings.[65] Somatostatin receptor scintigraphy has been used successfully to diagnose insulin-secreting tumors in a small number of dogs.[55] Noninvasive diagnosis of insulinoma can be challenging in some instances and leaves abdominal exploratory as a final diagnostic test and, hopefully, therapeutic option.

Treatment

Hypoglycemia truly is a medical emergency and should be treated immediately because neurological damage can progress rapidly. Prompt emergent care with intravenous administration of dextrose is recommended. Oral glucose solutions such as Karo syrup can be administered as intravenous access is in progress. However, oral solutions should not be administered to patients during a seizure or if the swallowing/gag reflex is compromised. Once intravenous access is secured, 0.25 to 0.5 g/kg of 50 per cent dextrose should be administered as a bolus over 3 to 5 minutes.[52,63] After bolus administration, the patient should be started on a continuous rate infusion of maintenance fluids with added 2.5 per cent dextrose.[52] Careful monitoring is warranted to ensure that hypoglycemia is corrected with fluid supplementation. Care also should be taken to avoid rapid increases in blood glucose that could initiate severe rebound hypoglycemia progressing to hyperglycemia/hypoglycemia cycles. Progressive hyperglycemia/hypoglycemia is life threatening because cerebral edema and an intractable seizure disorder may develop. Treatment of hyperglycemia/hypoglycemia cycles may require administration of glucagon, antiepileptics, glucocorticoids, diuretics, mannitol, and in the most severe cases, general anesthesia to control edema and seizures.[55]

For best long-term results, primary treatment of the underlying cause of hypoglycemia is recommended. For most tumors, surgical excision is recommended, with the exception of lymphoma. In those instances in which surgical management is not possible or fails to resolve hypoglycemia, other medical therapies can be administered. The most common medical therapy used to treat hypoglycemia is glucocorticoids. Glucocorticoids are insulin antagonists, and have a stimulatory impact on hepatic glycogenolysis (directly) and gluconeogenesis (indirectly).[55] Prednisone (0.25 to 1.0 mg/kg PO q12h) is administered at the lowest effective dose. Over time, dose escalation may be required.[55] Dietary manipulation also can play an important role in managing hypoglycemia medically. Frequent feedings of a diet that is high in protein, fat, and complex carbohydrates have been recommended.[55] Other recommended medical therapies include diazoxide (5 to 20 mg/kg PO q12h), octreotide (1 to 2 µg/kg SC q8-12h), and propranolol (0.2 to 1.0 mg/kg PO q8h).[55,58,63,65] These therapies generally are used if hypoglycemia is not controlled adequately with glucocorticoids and dietary management.

LOWER URINARY TRACT OBSTRUCTION

Etiology

Although inflammatory diseases of the bladder or cystoliths are far more common causes of dysuria and stranguria, tumors of the urinary tract should be considered as a differential diagnosis for cats presenting with signs of hematuria, stranguria, dysuria, and tenesmus.[66,67] Tumors of the feline urinary tract may originate from tissues of epithelial, mesenchymal, or hematopoietic origin.[68] The uroepithelium is at risk for developing malignant transformation because the mucosa is in regular contact with carcinogenic agents that have been concentrated in the urine, then retained for prolonged periods. Chronic inflammatory disease, carcinogens, viruses, drug metabolites, and parasites have been implicated as risk factors for the development of bladder neoplasia in human beings and dogs.[67] Specific risk factors for the development of lower urinary tract neoplasia have not been identified in cats. Lower urinary tract tumors have been reported in the bladder, urethra, prostate (in males), and vagina (in females).[69] Tumors occur more commonly in the bladder than other anatomical locations within the lower urinary tract. Unlike dogs, tumors appear to occur more commonly in the body of the bladder than in the trigone or urethra.[69] The reader is referred to Chapter 68 for a detailed discussion of lower urinary tract tumors.

Pathophysiology

Urinary tract obstruction is an emergent medical condition that can result in electrolyte and acid-base disorders, in addition to accumulation of toxic metabolic waste products. Postrenal obstructive uremia can develop within the first 24 hours after obstruction. Concurrent and ensuing dehydration, metabolic acidosis, hyperkalemia, hyperphosphatemia, and hypercalcemia can further destabilize the obstructed cat. Death can occur within 3 to 6 days of obstruction if appropriate therapies are not administered.[70,71] After resolution of obstruction, postobstructive diuresis develops because of the inability of the distal renal tubules to modulate water and sodium balance. Micturition dysfunction can result from decreased elasticity of the bladder, neuromuscular damage in the bladder wall, and urethral spasm. In some cases, renal failure may develop as a result of increased intrarenal pressure, electrolyte abnormalities, dehydration-related renal ischemia, and damage caused by cytokines.[71] As in dogs, tumors located in the trigone or neck of the bladder can cause ureteral or urethral obstruction.

Clinical Signs

Clinical signs of lower urinary tract neoplasia often are present for some weeks to months before progression to obstruction. Clinical signs result from the loss of volume capacity, decreased wall compliance, and functional or mechanical outflow obstruction. Because they often are indistinguishable from signs of other, more common causes of feline lower urinary tract disease, clinical signs of lower urinary tract neoplasia often are treated symptomatically, sometimes with apparent success, before the more ominous sign of obstruction is apparent.[67] Clinical signs of lower urinary tract neoplasia include hematuria, dysuria, stranguria, pollakiuria, tenesmus, and constipation. Clinical signs of urinary tract obstruction include anorexia, vomiting, weakness, bradycardia, enlarged urinary bladder, ascites (resulting from uroperitoneum), dehydration, and coma.[67,69,70]

Differential Diagnoses

Common differential diagnoses include interstitial cystitis, urolithiasis, and less commonly, bacterial infections and neoplasia.[67] Tumor types that have been reported in the feline lower urinary tract are listed in Table 64-2.[67,70]

Diagnosis

Cats with lower urinary tract obstruction should be evaluated promptly with serum chemistries to assess electrolyte abnormalities and abdominal radiographs to assess for bladder or urethral urolithiasis. Additionally, bladder wall mineralization (suggestive of neoplasia) and sublumbar lymphadenopathy may be identified on plain abdominal radiographs.[69] Evaluation of the urine sediment may be helpful in diagnosing infection and neoplasia. Cytology of urine sediment occasionally allows identification of malignant epithelial cells. Care should be taken not to overinterpret cytological findings of malignancy in the face of moderate to severe inflammation; epithelial cells may exhibit striking atypical or dysplastic features with concurrent inflammation (see Figure 68-1).[67] Samples also should be collected for culture and susceptibility testing. Sonography is an important noninvasive method of evaluating the kidneys, ureters, urinary bladder, proximal urethra, and sublumbar lymph nodes for the presence of a mass effect (Figure 64-12). Another benefit of sonography is that anesthesia usually is not required. This is an important consideration in the metabolically unstable patient with urinary tract obstruction. Sonography also aids in the detection of hydroureter and hydronephrosis resulting from obstruction of tumors in the trigone region (Figure 64-13). Sonography cannot distinguish between mass effects that are inflammatory in nature versus those that are neoplastic. That determination is made only based on cytology or histopathological sample evaluation (see Figure 68-3). In some instances, contrast radiography, contrast urethrocystography, or cystography may be used to identify a bladder or urethral mass.

Once a mass is identified, several methods have been described for tumor sampling including percutaneous needle aspirate with or without ultrasound guidance, transurethral

Table 64-2 | **Tumors of the Feline Lower Urinary Tract**

MALIGNANT TUMORS
Transitional cell carcinoma
Squamous cell carcinoma
Adenocarcinoma
Unclassified carcinoma
Lymphoma
Hemangiosarcoma
Myxosarcoma
Rhabdomyosarcoma
Prostate adenocarcinoma
BENIGN TUMORS
Papilloma
Cystadenoma
Fibroma
Leiomyoma

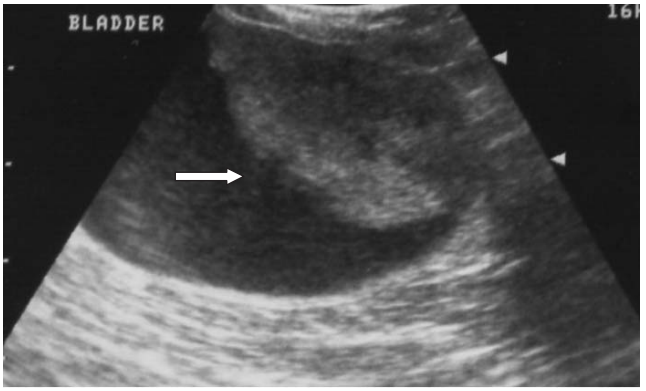

Figure 64-12. Ultrasound image of a large mass *(arrow)* in the trigone region of the urinary bladder that was causing clinical signs of hematuria, stranguria, and tenesmus. Transitional cell carcinoma was confirmed by ultrasound-guided percutaneous needle aspirate cytology.

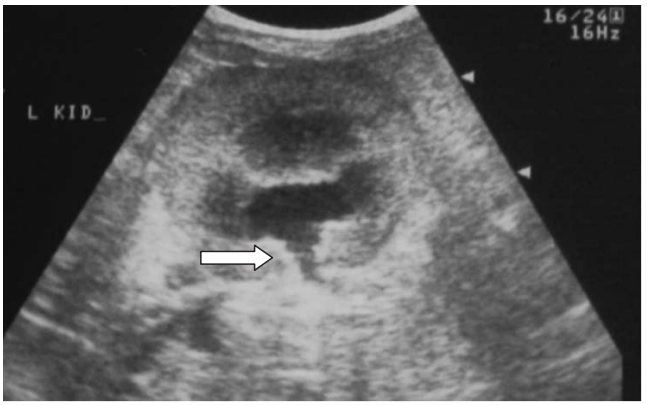

Figure 64-13. Ultrasound image of the left kidney of the same cat from Figure 64-12 showing hydronephrosis and hydroureter secondary to transitional cell carcinoma obstructing the left ureter at the bladder trigone.

catheter biopsy, cystoscopy in female cats or male cats that have previously undergone perineal urethrostomy, and cystotomy.[67]

Treatment

The goals of therapy in treating lower urinary tract obstruction should be to correct fluid, electrolyte, and acid-base disorders, in addition to reestablishment of urine outflow.[70]

Urethral catheterization and reverse flushing of saline into the urinary bladder typically relieves obstruction caused by urethral plugs. The same benefit of urethral flushing may not be expected in the case of obstruction caused by transmural or periurethral tissue masses.[70] In some instances, decompression cystocentesis may be required to empty the urinary bladder and stabilize the patient. Decompression cystocentesis can be performed safely in these patients, but risk factors should be considered before the procedure is performed. Potential adverse consequences include urine extravasation into the bladder wall or peritoneal cavity, injury to a potentially devitalized bladder wall, and potential tumor seeding along a needle tract.[70,76]

The procedure for decompression cystocentesis has been outlined in detail.[70] A 22-gauge or 23-gauge needle should be attached to one end of a flexible intravenous extension set. The opposite end of the extension set should be attached to a three-way stopcock and 35-mL or 60-mL syringe. The needle should be inserted through the ventral bladder wall midway between the bladder vertex and the bladder neck. The goal of decompression cystocentesis is to remove the majority of urine, while leaving 15 to 20 mL of residual volume. Care should be taken to keep the needle stable to avoid bladder laceration and to avoid excessive digital pressure on the bladder during stabilization.[70] A urine sample should be saved for diagnostic testing.

Placement of an indwelling urethral catheter (sterilized red rubber catheter) to be maintained and managed with a closed urine collection system is important in management of postobstructive diuresis. Techniques for urethral catheter placement have been described in detail.[70] However, in some instances it may not be possible to pass a catheter beyond an obstructive lesion, reobstruction may occur after removal of the indwelling catheter, or the bladder lumen may be filled with the mass effect. These situations dictate a grave prognosis because the use of palliative cystostomy tubes and urinary diversion procedures have not been attempted in cats. Urinary diversion has been tried in dogs and is reported to have numerous complicating sequelae.[67,72] In male cats with tumors in the very distal urethra, perineal urethrostomy may be performed.[67]

RESPIRATORY OBSTRUCTION AND DISTRESS

Etiology

Tumor growth in the upper or lower airways can result in respiratory distress because of the physical presence of the mass, a secondary inflammatory response, or obstruction of normal outflow of secretions.

Tumors of the respiratory tract may arise from epithelial tissues (adenomatous polyps, carcinoma, adenocarcinoma), connective tissues (chondrosarcoma, rhabdomyosarcoma, osteosarcoma), or from the hematopoietic system (lymphoma).[73,74] Respiratory tract tumors may be primary or metastatic and may be a component of larger systemic disease, as is often the case with lymphoma.[75] Respiratory tumors may occur at any point along the respiratory tract including the nasal passages, nasopharynx, oropharynx, larynx, trachea, bronchi/bronchioles, and pulmonary interstitium.

Clinical Signs

The cat presenting in respiratory distress has a breathing pattern and clinical signs that, in most circumstances, allow the clinician to localize the anatomical area affected. Loud breathing that can be heard without a stethoscope can be localized to the larger airways.[52] Stertor is a sound produced by a nasal or nasopharyngeal obstruction that sounds like a "snore."[74] Kirby, Rudloff, and Wilson[52] provide the following guidelines for evaluating breathing patterns of cats. Inspiratory stridor is localized to the larynx and pharynx. Expiratory stridor localizes to the intrathoracic trachea or bronchi. Rapid, shallow smooth breathing with abdominal and thoracic excursions in the same direction at the same time localizes to the pulmonary parenchyma. Short, choppy breathing with short inspiratory and expiratory times and abdominal and thoracic excursions in the opposite direction localizes to the pleural space. Short inspiratory and prolonged expiratory excursions with an abdominal push in the same direction at the same time are localized to

small airways.[52] In addition to changes seen in respiratory patterns, other clinical signs seen with respiratory tract obstruction include nasal discharge, tachypnea, lethargy, cyanosis, open-mouth breathing, weight loss, anorexia, nasal discharge (mucopurulent, hemorrhagic, or serous), sneezing, coughing, nasofacial deformity, epiphora, or change in voice or purr.[74,75]

Differential Diagnoses

Differential diagnoses for presenting clinical signs localized to the nasal passages include neoplasia, infectious diseases, inflammatory disorders, anatomical defects such as stenosis, or foreign bodies. Lymphoma is the most common neoplasm of the feline nasal cavity. Other tumors include adenocarcinoma, undifferentiated carcinoma, olfactory neuroblastoma, fibrosarcoma, chondrosarcoma, and chondroma. Differential diagnoses for infectious causes of nasal signs include viral, bacterial, and fungal organisms (see Chapter 38).[74,75]

Nasopharyngeal and oropharyngeal tumors associated with respiratory tract obstruction include lymphoma, adenocarcinoma, SCC, rhabdomyosarcoma, melanoma, and sarcomas.[76] Nasopharyngeal polyps are chronic inflammatory lesions arising from the mucosa of the eustachian tube.[77] Nasopharyngeal polyps are the second most common cause of stertor and nasal discharge in cats.[74,76] Other nonneoplastic causes of respiratory stridor/distress localized to the nasopharyngeal and oropharyngeal regions include foreign bodies, laryngeal paralysis, pharyngeal mucocoele, and nasopharyngeal stenosis.[75,78,79]

Tracheal tumors (lymphoma and epithelial tumors)[73] can present with either inspiratory or expiratory dyspnea depending on the anatomical location (cervical vs. intrathoracic) of the mass. Other differential diagnoses for tracheal causes of dyspnea include foreign body and tracheal tear or avulsion.[80-82]

Respiratory distress associated with primary lung tumors is rare. More commonly, respiratory signs (dyspnea, tachypnea, wheezing, coughing) associated with primary lung tumors are chronic and do not occur in all affected cats.[73] However, respiratory distress may be seen in cats with advanced pulmonary metastases. Other differential diagnoses of expiratory dyspnea of pulmonary origin include infectious causes (fungal, bacterial, protozoal, viral, or parasitic),[83] noncardiogenic pulmonary edema,[84] hemorrhage secondary to coagulopathy, asthma, and heart-related causes. In some instances, hyperthyroid cats experiencing "thyroid storm" may appear initially to be in respiratory distress (open-mouth breathing, panting).[75]

Diagnosis

Initial steps toward localization of the mass effect can be determined based on the observation of nasal discharge, loud breathing, stertor, inspiratory stridor, or expiratory stridor as described previously.[52] Thorough examination, including digital palpation of the soft palate and endoscopy of the oral cavity and pharyngeal region, with the patient under general anesthesia, is paramount for cats with clinical signs of inspiratory distress.[74] Other diagnostic tests that may be helpful to determine the cause of respiratory distress include thoracic radiographs, echocardiography, laryngeal sonography,[85] nasal radiographs, and advanced imaging such as CT or MRI. Once a tumor has been identified, samples should be collected for microscopic, cytological, or histopathological evaluation. Numerous methods have been described to collect cytological specimens including swab, lavage, traumatic flushing, pinch biopsies, and core biopsies.[75,77] Depending on the tumor location and its accessibility, one or more of these techniques may be applied for sampling.[75] Cytological changes associated with a number of feline nasopharyngeal diseases are well described in the second volume of *Consultations in Feline Internal Medicine*.[77]

Treatment

Emergency treatment of respiratory distress begins with oxygen support and reduction of the patient's level of anxiety. In some instances, administration of a mild sedative such as butorphanol (0.2 to 0.4 mg/kg IV or IM)[52] may lessen the patient's apprehension. Some patients with upper airway obstruction may require surgical extirpation of the obstructing mass (especially in cases of nasopharyngeal polyps or other pharyngeal masses) or emergency tracheostomy to open the airway. Advanced planning before induction of anesthesia is important. A laryngoscope and endotracheal tube (ET) should be readily available for intubation. In addition to an ET that is appropriate in size, smaller diameter ET tubes or a red rubber catheter (5 to 10 French) should be available for intubation in case of severe narrowing of the airway in the pharyngeal/laryngeal region. Antibiotic and prednisone (0.5 to 1 mg/kg PO q12h) therapy may lessen inflammation and nasal discharge secondary to neoplasia in the nasal passages. Chemotherapy (L-asparaginase 400 IU/kg SC, vincristine 0.025 mg/kg IV, and dexamethasone 0.25 mg/kg IV) also may be used as an emergency treatment of nasopharyngeal lymphoma.[86]

Treatment of intrathoracic causes of respiratory distress also begins with oxygen therapy and diminishing levels of anxiety. No effective definitive therapies for metastatic pulmonary neoplasia exist. Symptomatic therapies to be considered include glucocorticoids (prednisone 1.0 to 2.2 mg/kg SQ or IV q12h; dexamethasone 0.1 to 0.22 mg/kg SQ or IV q12-24h) as anti-inflammatory therapy, and bronchodilators (aminophylline 5 mg/kg IV slowly or terbutaline 0.01 mg/kg SC or IM).[83] Response to these therapies is somewhat variable, with an overall poor prognosis for long-term survival. If a positive response to injectable corticosteroids and bronchodilators is demonstrated, oral therapy such as terbutaline (0.0312 to 0.0625 mg per cat PO q8-12h) or theophylline (Theo-Dur 20 mg/kg PO q24h, AstraZeneca, Wilmington, DE) can be substituted.[83]

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Chapter 65

Medical Record Keeping for the Oncology Patient

Kenita S. Rogers and Diane Green

CHEMOTHERAPY ADMINISTRATION FORM

CHEMOTHERAPY TREATMENT LOG SHEET

MASS ASSESSMENT (MAPPING) FORM

Organized, descriptive medical records can be a tremendous asset to the busy practice that cares for a substantial number of cancer patients, particularly those receiving chemotherapy. Several specific forms can be customized to improve accurate communication between the multiple doctors and technicians who may be caring for an individual patient within a practice. Following an outline of these forms consistently can help to prevent dosing and administration errors, ensure that all personnel are aware of the drug and dose the patient should be receiving, provide a location where specific notes regarding the animal's care can be found, and facilitate accurate recording of the locations and dimensions of multifocal masses. This chapter describes some of the forms that may be helpful in a practical setting.

CHEMOTHERAPY ADMINISTRATION FORM

The front of the chemotherapy administration form (Figure 65-1) is designed to identify the patient; highlight complete blood count (CBC) and other pertinent test results; note the current weight of the patient in pounds, kilograms, and meter squared (m^2) body surface area; and note any premedications given, including antihistamines, corticosteroids, and sedatives. The form also is useful for listing the specific chemotherapy drug administered, route of drug administration, precise catheter placement location, information about drug infusion and catheter removal, and current tumor size assessment. In addition, it provides a reminder that more than one person should calculate the chemotherapy drug dose independently before administration.

Identifying the patient on the form is particularly important for the busy practice that may administer chemotherapy to more than one patient daily (see shaded box in Figure 65-1). Ideally, the patient should be identified with a case number, pet name, owner name, age, breed, sex, and diagnosis. The date of chemotherapy administration should be included, because over time, the chemotherapy administration forms are kept in sequential order.

The portion of the form dedicated to test results can be customized to fit the individual patient or drug being administered, but CBC results are necessary for all potentially myelosuppressive drugs. In addition, some drugs are nephrotoxic, such as doxorubicin (specific toxicity for cats) and cisplatin (administered only in dogs), so a location to list renal parameters including blood urea nitrogen, creatinine, and urine specific gravity is useful. For potentially hepatotoxic drugs such as lomustine (CCNU), a line could be added if the clinician wished to monitor hepatic enzyme changes. For any patient with preexisting cardiac disease and all canine patients receiving doxorubicin, the results of cardiac status on complete physical examination, electrocardiogram, and echocardiogram, if indicated, can be recorded on this portion of the form.

The most common mistake made in chemotherapy administration is dosing error. Some of these mistakes are made because the drug dose in m^2 is calculated incorrectly. This mistake typically is made because the caregiver weighs the patient in pounds and forgets to convert this weight to kilograms before using the body surface area (m^2) conversion chart. This mistake roughly doubles the calculated dose of chemotherapy to be administered. For many chemotherapeutic agents, this degree of overdose can have catastrophic adverse results.

One way to avoid this error routinely is to use the form to force the calculation from pounds to kilograms to m^2. Another routine practice designed to prevent dosing error is to require that at least two, and preferably three, persons calculate the dose independently and then compare their results. The final line on the form provides a space for each of these persons to initial that they have performed this calculation and that they agree with the listed results.

Premedication may be necessary in some oncology patients. Common indications would include administering diphenhydramine before repeated administration of L-asparaginase, before treating a patient with systemic mast cell disease, and before doxorubicin administration in dogs. In some patients, sedation is required to facilitate safe and efficient drug administration. Regardless of the indication, the dose and form of the medication should be recorded and the time before chemotherapy drug administration noted.

Recording the specific drug administered is particularly important in protocols in which several drugs are used in combination. If a new clinician is evaluating the case, this

CHEMOTHERAPY ADMINISTRATION

CBC: Date _____ RDVM ☐ TAMU ☐

WBC/Neutrophils: _____ / _____
PCV: _____
Platelets: _____
BUN/Crea: _____ / _____
Urine SG: _____

ECG[ ] _____ Echo _____
WT: _____ lbs
_____ kg
_____ M^2

ADMINISTRATION DATE: _____

PREMEDICATIONS

DIAGNOSIS: _____

Benadryl: _____ mg. IV IM SQ _____ AM PM _____ minutes pre-chemo
_____ mg. IV IM SQ _____ AM PM _____ minutes pre-chemo

CHEMOTHERAPY

Drug used: _____

Butterfly catheter [ ] Indwelling catheter [ ] Cath. sz. _____ SQ [ ] Oral [ ]

Dose: _____ mg per M^2 or kg = _____ mg Dose given _____

Diluted in _____ ml NaCl SQ injection given: R L _____

Catheter placed in R L _____ Vein. Flushed with _____ ml NaCl before administration of chemotherapy.

Drug infused over _____ minutes.

Catheter was flushed with _____ ml NaCl post-administration. It was then pulled, and a light pressure bandage was applied.

MARKER LESION MEASUREMENTS _____

COMMENTS _____

Dose verified by:

_____ DVM _____ Tech _____ RPh _____ Student

Figure 65-1. Chemotherapy administration form (front).

information can highlight at what point this patient is within the ongoing protocol and which drug should be administered next. Indicating the route of administration is particularly important for drugs such as cyclophosphamide, which can be supplied in more than one form. It also is helpful to confirm the proper route to ensure avoidance of this type of administration mistake.

The dose of drug and dose calculation should be identified on the form. Calculated doses may need to be increased or decreased modestly because the supplied concentrations of the

CONVERSION OF BODY WEIGHT IN KILOGRAMS TO BODY SURFACE AREA

Kg	M^2	Kg	M^2
0.5	0.06	26.0	0.88
1.0	**0.10**	**27.0**	**0.90**
2.0	0.15	28.0	0.92
3.0	**0.20**	**29.0**	**0.94**
4.0	0.25	30.0	0.96
5.0	**0.29**	**31.0**	**0.99**
6.0	0.33	32.0	1.01
7.0	**0.36**	**33.0**	**1.03**
8.0	0.40	34.0	1.05
9.0	**0.43**	**35.0**	**1.07**
10.0	0.46	36.0	1.09
11.0	**0.49**	**37.0**	**1.11**
12.0	0.52	38.0	1.13
13.0	**0.55**	**39.0**	**1.15**
14.0	0.58	40.0	1.17
15.0	**0.60**	**41.0**	**1.19**
16.0	0.63	42.0	1.21
17.0	**0.66**	**43.0**	**1.23**
18.0	0.69	44.0	1.25
19.0	**0.71**	**45.0**	**1.26**
20.0	0.74	46.0	1.28
21.0	**0.76**	**47.0**	**1.30**
22.0	0.78	48.0	1.32
23.0	**0.81**	**49.0**	**1.34**
24.0	0.83	50.0	1.36
25.0	**0.85**	**51.0**	**1.38**

PRE-CHEMO WORK-UP

- **CBC:** All drugs. Obtain via jugular vein.
- **Doxorubicin:** Canine: cardiac work up. Feline: renal evaluation.

ADMINISTRATION CONSIDERATIONS

- **First stick catheters** on all IV preparations. Prior to administration, flush with saline to assure that it is a clean stick, and after infusion to clear all drug from the needle or catheter tip.
- **Doxorubicin:** Canine–premedicate with diphenhydramine (2 mg/kg) +/− steroids.
- **Carboplatin:** Administer with plastic hubbed needles.
- **Agents to be infused:** Dilute in saline.
  <5 kg: 30 mls.
  5-20 kg: 50 mls.
  >20 kg: 100 mls.
- **Oral cyclophosphamide:** Check a CBC prior to administering the third dose during the first cycle of treatment.
- **Lomustine:** Recheck a CBC at one and two weeks post-administration during first cycle.

DRUG	DOSE/PREPARATIONS	ADMINISTRATION
DOXORUBICIN	<10 kg: 1 mg/kg >10 kg: 30 mg/m^2 10 mg vials	Diluted in saline, infuse over a minimum of 15 minutes via a "first stick" indwelling IV catheter
CARBOPLATIN	Canine: 250-300 mg/m^2 Feline: 150-200 mg/m^2 50 mg and 150 mg vials	Diluted in saline, infuse over 15 minutes via an indwelling IV catheter
CYCLOPHOSPHAMIDE	Canine: 60 mg/m^2 Feline: 50 mg/m^2 25 mg and 50 mg tablets	Give orally once daily for four days. Check a CBC prior to dose number one and three in the first cycle
LOMUSTINE	Canine 60 mg/m^2 10 mg and 40 mg capsules	Give orally in **one** dose every four weeks
VINCRISTINE	0.5-0.7 mg/m^2 1 mg/ml vials	Bolus IV via a "first stick" butterfly catheter

Figure 65-2. Chemotherapy administration form (back).

drug may not be matched conveniently with the calculated dose. Altering the actual dose administered also may be based on historical knowledge of how this particular patient responded when the calculated dose was administered during a previous cycle. For example, a decision may be made to lower the drug dose at the next cycle because this patient experienced a dangerous degree of myelosuppression or unacceptable gastrointestinal toxicity at the calculated dose. The reason for the altered dose in this patient can be highlighted on the form where the actual dose administered is listed and will be a reminder to the caregiver when the patient is treated again. If a drug such as doxorubicin or carboplatin is administered in an infusion, the

volume of saline with diluted drug and the number of minutes that was required for drug infusion can be listed.

Documentation of the site of drug administration is particularly important in the event of an adverse reaction. Several chemotherapy drugs in common use (doxorubicin and related compounds, vincristine, vinblastine) are associated with the potential for extravasation injury if there is perivascular leakage. This form also would be an appropriate place to identify which veins had become difficult to access because of prolonged use. This information can be valuable to the clinician performing the next chemotherapy treatment in this patient. One important means of preserving use of the peripheral veins for as long as possible is to insist on jugular venipuncture for pretreatment blood collection.

In some clinical cases, demonstrating changes in a measurable marker lesion is used to assess the efficacy of a chemotherapy drug before administering additional doses. Measurements of the lesion before drug administration and at the time of the next treatment help in the decision-making process. In addition to marker lesion measurements, other pertinent comments can be placed at the bottom of the form. These notes may address need for sedation on subsequent visits, new medical conditions, owner concerns, or plans for future treatment.

The back of the chemotherapy administration form (Figure 65-2) can include helpful charts, comments, and reminders. Some examples would be a conversion chart for body surface area, reminders about requirements for prechemotherapy workup, specific drug administration tips, and doses of the chemotherapy agents used most commonly in individual practice settings. It also is helpful to make the chemotherapy administration sheet a different color than others in the medical record so that it is easy to identify and access.

CHEMOTHERAPY TREATMENT LOG SHEET

Many patients have prolonged courses of chemotherapy prescribed to treat their diagnosed malignancy. A common example is lymphoma patients that may receive a series of drugs in a rotating protocol for a year or more. To ensure each clinician and technician who may be involved in chemotherapy administration understands the patient's progression within the prescribed protocol, a log sheet can be placed in the front of the medical record as a quick reference (Figure 65-3). The information on this sheet is transcribed at each visit from the chemotherapy administration sheet (see Figure 65-1). Suggested information to place on the log sheet would include patient and client identification, the date of drug administration, current weight of the patient, which drug was given, calculated and administered drug dose, any toxicities since the last course of therapy including adverse reactions reported by the owner and evidence of neutropenia on post-treatment CBCs, and whether sedation was required for this patient. For this log sheet to be helpful, it must be updated by the technician or clinician overseeing the case at the time of each chemotherapy treatment.

CHEMOTHERAPY TREATMENT LOG SHEET

DATE	WT.	CHEMOTHERAPY AGENT	CALC. DOSE	DOSE ADMIN.	TOXICITIES	COMMENTS	SEDATION AGENT/DOSE

Figure 65-3. Chemotherapy treatment log sheet.

MASS ASSESSMENT (MAPPING) FORM

Accurate, objective assessment of changes in the size of mass lesions should be part of the complete physical examination and form the basis for determining current tumor growth rate and efficacy of a chosen therapeutic modality (Figure 65-4). One example of the use of these data would be in a patient with an unresectable soft tissue sarcoma. These tumors often are poorly responsive to chemotherapy, and the owner will wish to make decisions for their pet based on accurate assessment of the benefits and risks of a particular treatment. If the decision is made to try a course of chemotherapy, the mass should be measured as accurately as possible in three dimensions and the results recorded on the mass assessment form. At the time of the next chemotherapy treatment, the mass can be measured again. The results are compared to help provide information regarding the responsiveness of this particular tumor to the administered drug.

Another clinical situation in which this form can be useful is for the patient that develops numerous cutaneous and subcutaneous nodules sequentially over months and years. Development of 10 to 30 nodules during their lifetime is a common occurrence in elderly dogs, and some cats also develop multiple cutaneous and subcutaneous masses. Each of these masses may be described on the mass assessment form and "mapped." Figure 65-4 illustrates a form that can be used to list the assigned number of the lesion, a brief description of the mass and its location, recording of three-dimensional measurements, and results of cytology, if performed. Figure 65-5 is a line drawing of the cat that can be used to supplement the mass assessment chart by helping to identify the approximate location of each mass found on physical examination. For the set of patients that are prone to multiple mass development, having these forms within the medical record, showing which masses were already identified, measured, and aspirated at earlier visits can save a tremendous amount of time for the veterinarian. For

Mass Assessment

Date ____________

LESION Number	CUTANEOUS LOCATION & DESCRIPTION	MEASUREMENTS	CYTOLOGY RESULTS
	Epidermal ☐ Dermal ☐ SQ ☐	Medial/lateral Cranial/caudal Depth Ventral/dorsal	
	Epidermal ☐ Dermal ☐ SQ ☐	Medial/lateral Cranial/caudal Depth Ventral/dorsal	
	Epidermal ☐ Dermal ☐ SQ ☐	Medial/lateral Cranial/caudal Depth Ventral/dorsal	
	Epidermal ☐ Dermal ☐ SQ ☐	Medial/lateral Cranial/caudal Depth Ventral/dorsal	
	Epidermal ☐ Dermal ☐ SQ ☐	Medial/lateral Cranial/caudal Depth Ventral/dorsal	
	Epidermal ☐ Dermal ☐ SQ ☐	Medial/lateral Cranial/caudal Depth Ventral/dorsal	

Figure 65-4. Mass assessment form for mapping.

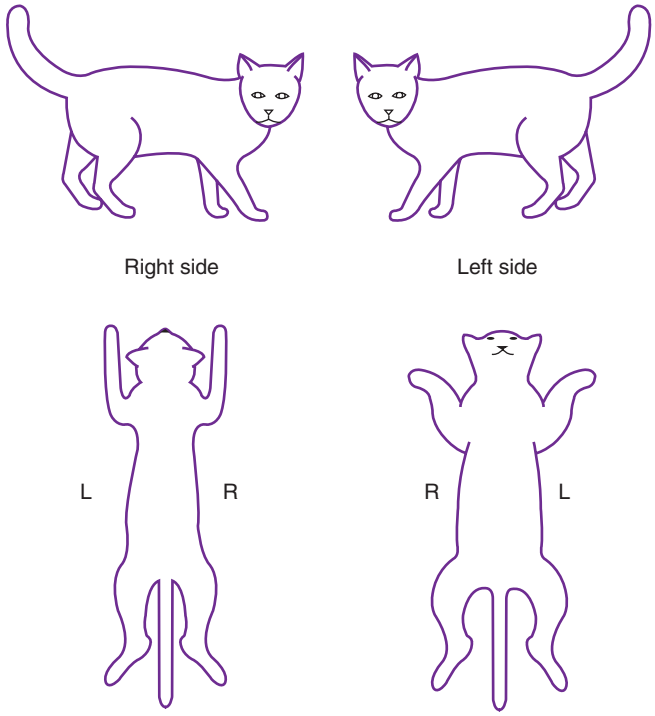

Figure 65-5. Feline lesion location chart.

the busy clinician and most owners, it is difficult to remember over time exactly where each of these masses was located and their precise size. Recording objective data on this sheet can prevent redundant effort. With use of this chart, subsequent visits can focus on identifying new lesions and remeasuring only the ones that appear to have changed in size or texture. Every new nodule deserves cytological assessment at least once. Results from this testing can be placed in the permanent medical record on this form. For animals that develop large numbers of these masses on a routine basis, the mapping procedure can take a great deal of time, and this procedure should be appropriately charged for, justified by being an important part of a complete medical record for the pet.

Precise, objective, and consistent medical records are supportive documents for providing excellent care to the veterinary oncology patient. These records should be customized to the type of cancer patients seen and treated in the practice. In general, records should be developed that focus on prevention of errors, identification of preventable problems, allowance of consistent patient evaluation, and facilitation of the most efficacious therapy possible. Routine use of forms developed specifically for oncology patients can help meet the diagnostic and treatment goals of the practice.

Chapter 66

EXTRANODAL LYMPHOSARCOMA

Annette N. Smith

Lymphoma, or lymphosarcoma (LSA), is the most common tumor diagnosed in cats. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) infections have been associated with the development of LSA, although cats without retroviral exposure also can develop LSA spontaneously.[1] Cats with FeLV have a sixtyfold greater likelihood of developing LSA and cats with FIV have a fivefold greater likelihood than cats that are FeLV/FIV–negative.[2] Cats infected with both viruses have an eightyfold chance of developing LSA, compared with cats infected with neither virus.[2] However, the tumors of many seronegative cats contain viral sequences or membrane proteins detected through Western blot, polymerase chain reaction (PCR), and immunohistochemical techniques,[3-8] which indicates a potential role of retroviral exposure in LSA development even in cats that clear initial infection. Incidence of LSA appears to reflect the incidence of FeLV and FIV infection, and with decreasing incidence of infection because of more aggressive testing for and management of retroviruses, the types of LSA seen in the United States are shifting to those seen most classically in FeLV-negative cats.[9,10] Currently, gastrointestinal (GI) LSA is the site diagnosed most commonly in cats.

Advances in immunohistochemical techniques have demonstrated fewer T-cell LSAs in cats than has been presumed historically. The incidence of LSA that displays T-cell characteristics ranges from 25 to 67 per cent; those with B-cell characteristics range from 27 to 70 per cent; and null-cell LSA makes up 4 to 6 per cent of cases.[6,10,11] FeLV status does not appear to affect immunophenotype, because B-cell and T-cell tumors are found in equal incidence in FeLV-positive cats.[6] Instead, location appears to be the most important determinant of immunophenotype: cutaneous tumors primarily are T-cell in origin and GI tumors primarily are B-cell.[6] Most feline LSA is of intermediate grade (35 per cent) or high grade (55 per cent), with only 10 per cent of tumors considered well differentiated or low grade.[12] A specific subtype of GI LSA, described as LSA of large granular lymphocytes (LLGL), appears to be of cytotoxic T-cell or natural killer cell origin[13,14] and makes up approximately 10 per cent of feline GI LSA.[13] LLGL was described previously as large granular lymphoma or neoplasm of globule leukocytes,[15,16] but immunohistochemical staining has demonstrated that these entities are of similar origin.

DIAGNOSIS AND STAGING

Once LSA has been confirmed through histopathology or cytology of the affected organ, complete staging is recommended to determine disease extent (Table 66-1). Complete blood count (CBC), serum chemistry, and urinalysis findings usually are nonspecific but may include a regenerative or nonregenerative anemia,[17,18] neutrophilic leukocytosis, lymphocytosis, thrombocytopenia,[17] hypoalbuminemia, hyperglobulinemia,[17] hypercalcemia,[17,19] and/or prerenal or renal azotemia, depending on the primary anatomical site of the tumor and paraneoplastic effects. Hypercalcemia of malignancy is more rare in cats than in dogs with LSA, and other causes of hypercalcemia besides LSA also should be considered when this abnormality is found (Table 66-2) (see Chapter 17).

FeLV and FIV testing is useful to help an owner determine whether to treat a cat with LSA, because the prognosis historically has been poorer in FeLV-infected patients as a result of the debilitation often caused by concurrent FeLV-related diseases. In an apparently healthy FeLV-positive cat without concurrent FeLV-related disease (with the exception of the LSA), remission can be achieved at a rate similar to FeLV-negative patients, but owners should be made aware of the concurrent FeLV-related issues. Although not related to LSA per se, serum thyroxine (T_4) testing should be performed in all older cats to rule in or rule out concurrent hyperthyroidism (see Chapter 21).

Thoracic radiographs may reveal mediastinal, sternal, and/or perihilar lymphadenopathy, in addition to pulmonary nodular disease (as opposed to the diffuse pulmonary pattern often seen in dogs).[20] Imaging of the abdomen by radiographic means has been replaced largely by ultrasonography. Abdominal radiographs are useful in identification of GI obstructive lesions and can identify mass lesions, although identification of specific organ sources may not be possible. Peritoneal effusion also can be identified on survey radiographs. Advantages of ultrasonography include its noninvasive nature, lack of exposure to ionizing radiation, and elimination of the need for administration of contrast agents. Ultrasound allows for the evaluation of the internal structure of organs that may be infiltrated by tumor without demonstrating organomegaly, such as spleen, liver, kidneys, and mesenteric lymph nodes. Classically, LSA appears as diffuse or focal hypoechogenic areas within organs. Suspected LSA in liver, spleen, kidneys, intestines, and lymph

nodes should be confirmed with cytology or histopathology because other causes of hypoechogenicity are possible, and LSA infiltration can be present despite normal organ architecture.[21] Abdominal ultrasonography also is useful in guiding organ aspirates or biopsies.[22] Abdominal ultrasonography is less effective than radiography for the systematic evaluation of the entire GI tract (GIT), because luminal gas and peristalsis can obscure images and localization of a specific area of the small intestine is difficult. However, contrast radiography can eliminate some of these disadvantages with consistent evaluation of the entire GIT.

Bone marrow cytology can be useful in determination of the hematological reserves, especially in a FeLV-positive cat, and function as an easily obtainable site for identification of occult LSA (e.g., 70 per cent of cats with spinal LSA have concurrent bone marrow involvement even with normal peripheral blood smears).[23]

Table 66-1 | **Tests for Staging Feline Patients with Lymphosarcoma**

Complete blood count
Serum chemistry panel
Urinalysis
FeLV/FIV serology
T_4 (cats older than 5 years)
Three-view thoracic radiographs
Abdominal radiographs and/or abdominal ultrasound +/– organ aspiration, cytology and/or biopsy
Bone marrow aspirate
Sampling/imaging of other sites as suggested by clinical signs or physical examination (e.g., CSF tap, myelography, CT scan, MRI, nasal biopsy, skin biopsy, echocardiography, EKG)

Table 66-2 | **Differential Diagnoses for Feline Hypercalcemia***

Lymphosarcoma
Squamous cell carcinoma
Multiple myeloma
Other neoplasms (leukemia, osteosarcoma, fibrosarcoma, undifferentiated sarcoma, bronchogenic carcinoma)
Chronic renal failure
Idiopathic
Granulomatous disease (including cryptococcosis)
Hyperparathyroidism
Hypoadrenocorticism
Hypervitaminosis D

*See also Chapter 17.

TREATMENT AND PROGNOSIS

Because LSA is considered to be a systemic disease, chemotherapy is the mainstay of treatment (Tables 66-3 through 66-7). Surgery rarely is useful, except as a diagnostic tool. Radiation therapy may be useful palliatively or potentially curatively when solitary/localized tumors exist. Immunotherapy with various blood components,[24,25] *Staphylococcus aureus* components,[26-30] fibronectin,[31] acemannan,[32] and immunoregulin[33] have been investigated to varying degrees. Although some of these treatments are useful in clearing FeLV antigenemia and/or causing remission of LSA, no practical or commercially available immunotherapies are recommended at this time.

Supportive care, including fluids, appetite stimulants, antiemetics, and feeding tubes as necessary, is important in managing the feline cancer patient, especially those debilitated at diagnosis (see Chapters 69 and 70). Pathophysiology, diagnosis, treatment, and prognosis relating to the individual anatomical sites of extranodal lymphoma are addressed below.

Table 66-3 | **COP +/– Doxorubicin Protocol**

	WEEK GIVEN																			
DRUG DOSE	**1**	**2**	**3**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**	**31**	**34**	**37**	**40**	**43**	**46**	**49**	**52**
Vincristine 0.6-0.75 mg/m² IV	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cyclophosphamide 200-300 mg/m² PO (to nearest 25 mg)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prednisone 10 mg PO daily	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

+/– doxorubicin at 20-25 mg/m² IV q3 weeks for 2 to 8 treatments as maintenance once CR is achieved.

Table 66-4 | **VCM +/– Cytosine Arabinoside Protocol**

	WEEK GIVEN							
DRUG DOSE	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Vincristine 0.025 mg/kg IV	X		X		X		X	
+/– L-asparaginase 400 U/kg IM or SQ (then PRN for relapse)	X							
Cyclophosphamide 10 mg/kg IV		X				X		
Prednisone 5 mg/cat or 2 mg/kg PO q24h (continuously or prn for relapse or poor clinical response)								
Methotrexate 0.8 mg/kg IV or PO (IV for GI LSA to prevent GI toxicoses)				X				X
Cytosine arabinoside 600 mg/m² SQ, divided into two daily doses *Substituted for cyclophosphamide after CR achieved*								

Protocol repeated from week 5 until relapse or cure (2 years CR).

Table 66-5 | **University of Wisconsin-Madison Long-Term Maintenance Protocol**

	WEEK GIVEN																							
DRUG DOSE	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**
Vincristine 0.025 mg/kg IV	X		X			X		X			X	X			X				X						
L-asparaginase 400 U/kg IM	X																								
Cyclophosphamide 250 mg/m^2 IV				X					X																
Doxorubicin 20 mg/m^2 IV																	X								
Methotrexate 0.8 mg/kg IV																									
Prednisone 2 mg/kg PO q24h	X	X																							
Prednisone 1 mg/kg PO q24h			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 66-6 | **Animal Medical Center Protocol (for Alimentary LSA)**

	WEEK GIVEN													
DRUG DOSE	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Vincristine 0.025 mg/kg IV	X			X				X				X		
L-asparaginase 400 U/kg IM	X													
Cyclophosphamide 10 mg/kg IV		X			X					X				
Doxorubicin 20 mg/m^2 IV			X			X								
Methotrexate 0.8 mg/kg IV														X
Prednisone 5 mg/cat PO q24h	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Repeat weeks 8 to 14 for 12 months, then same drugs every 3 weeks for 6 months, then every 4 weeks for 6 months.

Table 66-7 | **Animal MOPP Protocol**

	WEEK GIVEN							
DRUG DOSE	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Vincristine 0.75 mg/m^2 IV		X			X	X		
Mechlorethamine HCl 3 mg/m^2 IV	X	X			X	X		
Procarbazine 10 mg/cat PO q24h for 14 days	X	X			X	X		
Prednisone 5 mg/cat PO q12h for 14 days	X	X			X	X		

Cycle repeats continuously every 4 weeks, until disease progression.

Mediastinal Lymphosarcoma

Mediastinal LSA (also called thymic LSA), once described as the most common form of LSA in cats, is now decreasing in incidence, because FeLV infection is strongly associated with its development. Most patients are young, with a median age of less than 5 years, and Siamese or Oriental purebreds may be at higher risk. Affected cats present typically with acute signs of dyspnea, secondary to a large space-occupying intrathoracic mass or pleural effusion. Other presenting complaints noted by owners may include regurgitation/vomiting, dysphagia, cough, anorexia, weight loss, enlarged lymph nodes, and ptyalism. On physical examination, an incompressible cranial thorax, a mass at the thoracic inlet, or auscultation of dull cranioventral lung fields may be noted. Peripheral lymphadenopathy, usually associated with the head, neck, or axilla, also may be found.

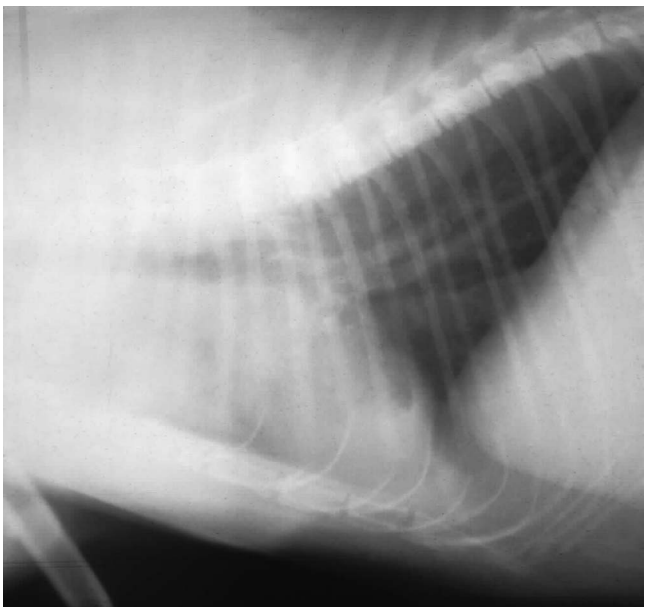

Figure 66-1. Lateral thoracic radiograph demonstrating a cranial mediastinal mass in a FeLV-positive cat. Lymphosarcoma was diagnosed.

Acute management should include oxygen therapy and thoracentesis before the thorax is imaged through radiology and thoracic ultrasound. A cranial mediastinal mass that displaces the trachea dorsally and the heart caudally is seen readily on thoracic radiographs (Figures 66-1 and 66-2).

Diagnosis may be made through evaluation of pleural fluid obtained by thoracentesis or fine-needle aspiration

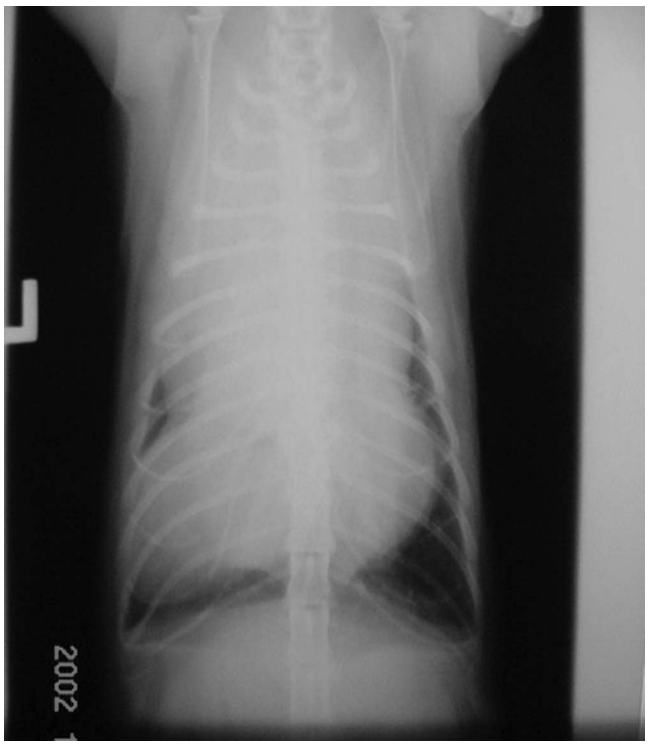

Figure 66-2. Ventrodorsal view of the cat shown in Figure 66-1.

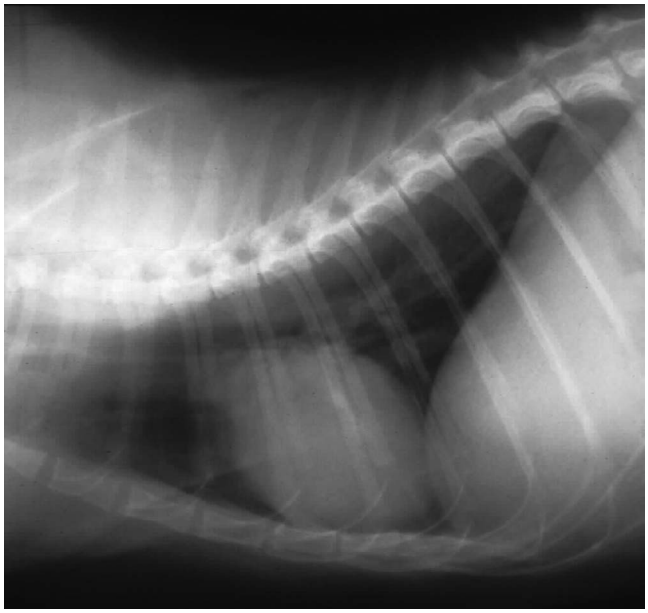

Figure 66-3. Lateral thoracic radiograph of the cat shown in Figures 66-1 and 66-2 after three fractions of radiation therapy, which demonstrates complete remission of the mediastinal LSA.

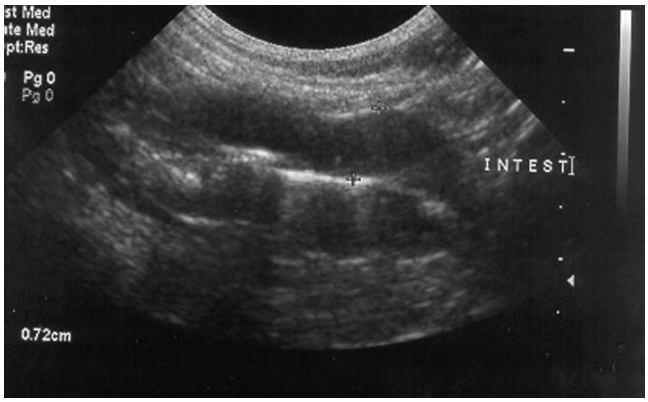

Figure 66-4. Ultrasound image showing hypoechoic thickening of the small intestinal wall with loss of architecture in a cat with intestinal LSA.

cytology/biopsy of the cranial mediastinal mass (blind or ultrasound-guided), which usually demonstrates large lymphoblasts. Small-cell (lymphocytic) LSA may require histopathology of biopsy samples to confirm the diagnosis because thymoma remains a differential diagnosis. Mediastinal LSA usually is T-cell based on immunohistochemistry, although older cats may have B-cell LSA.[10,11] Phenotype does not appear significant prognostically.

Currently, combination chemotherapy alone appears to induce remission in approximately 50 to 90 per cent of patients for a median of 2 to 6 months, although radiation therapy may be useful in inducing rapid remissions (Figure 66-3). The risk of sedating a dyspneic cat should be considered before radiation is recommended. Whether the addition of radiation to chemotherapy increases remission and survival time remains to be determined. Cats with localized disease that are FeLV-negative and achieve a complete remission (CR) have the best prognosis.

Alimentary Lymphosarcoma

Alimentary LSA is now considered to be the most common form of LSA seen in cats.[10,20] It usually is associated with FeLV-negative status based on serology (PCR positivity is more frequent)[3,10,34-36] and is seen in older cats (median age 10 to 12 years).[10,20,34-36] The small intestine is involved in the majority of patients (50 to 80 per cent), followed by the stomach (25 per cent) and cecum/colon.[34,36]

Clinical signs are related to the GIT and often include vomiting, weight loss, and/or diarrhea, in addition to nonspecific findings of anorexia, lethargy, depression, weakness, pica, and abdominal swelling.[35-37] Additional signs may be related to other systemic organ involvement. On physical examination, a distinct abdominal mass may be felt, or the bowel loops may be thickened diffusely.[36,38] Mesenteric lymphadenopathy resulting from tumor involvement or reactive hyperplasia also may be found.

Abdominal ultrasound, endoscopy, and surgical biopsy have been used as diagnostic tools to help differentiate LSA from other primary GI diseases. Abdominal ultrasonographic findings in cats with GI LSA (Figure 66-4) can include focal or diffuse wall thickening, wall hypoechogenicity, partial or complete disruption of wall layers, and localized hypomotility.[39,40] Mesenteric lymphadenopathy[39,40] and peritoneal effusion[39] also may be seen (Figure 66-5). Ultrasound-guided percutaneous fine-needle aspirates or automated Tru-cut microcore biopsies can be performed for presumptive or definitive diagnosis.[22,39-41] GI LSA is suggested by homogeneous hypoechogenicity, smooth margination, and symmetrical masses with complete loss of architecture, as opposed to other GI diseases, including other neoplasms.[40] When only superficial endoscopic biopsies

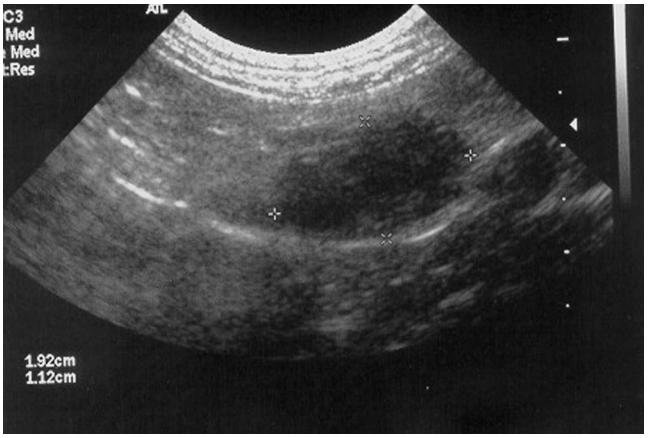

Figure 66-5. Ultrasound image demonstrating an enlarged, hypoechoic mesenteric lymph node infiltrated with LSA.

are obtained for diagnosis, GI LSA can be difficult to differentiate from inflammatory bowel disease and food intolerance,[42] which prompts some clinicians to recommend that full-thickness surgical or ultrasound-guided biopsies should be used for definitive diagnosis whenever possible.[43]

Therapy for GI LSA probably should be based on histopathological grade of the tumor. Cats with low-grade lymphocytic LSA can respond long term (years) with relatively minor chemotherapeutic intervention, such as chlorambucil and prednisone.[38] COP therapy, and doxorubicin as a single agent or as a maintenance therapy, have been used for GI LSA, with mixed results. Some authors suggest that doxorubicin always should be included in LSA protocols, whereas others have found COP therapy highly efficacious.[10,34-36,44-48] Median remission durations of 4 to 10 months have been reported in cats that achieve CR (approximately 32 to 70 per cent of patients). Some cats are refractory to any type of chemotherapy, with survival times measured in weeks.[34,36] CCNU (50 to 60 mg/m^2 PO every 3 to 6 weeks) has been used with some success by the author in the rescue setting, as has the MOPP protocol (see Table 66-7).

Prognostically, response to therapy seems to be most important, with those cats that achieve CR having much longer median survival times as opposed to those cats that achieve partial remission (PR) or stable disease (SD).[34-36] Argyrophilic nucleolar organizer region (AgNOR) staining as measurement of proliferative activity in tumor cells has been used as a prognostic indicator in some neoplastic conditions, but neither AgNOR counts nor AgNOR size has been useful to predict response to treatment or survival times in cats with intestinal LSA.[10,34]

Lymphoma of LLGL has been described as a less common subtype of GI LSA, which affects older FeLV-negative cats and causes palpable abdominal masses of the mesenteric lymph nodes or intestines.[15,49] Infiltration of other intraabdominal organs (large intestine, stomach, liver, spleen, kidney, and pancreas) has been seen, in addition to mediastinal masses and pleural effusion. Other systemic organ involvement also can occur as with any other LSA subtype, which prompts the recommendation of complete staging (see Table 66-1). Clinical signs usually are nonspecific and include weight loss, anorexia, and vomiting. Lethargy, diarrhea, icterus, and hematuria are seen less commonly. Intestinal perforation may occur.[14,50] LGLs may be seen in the peripheral blood, although normal cats also may have 3 to 13 per cent circulating LGLs.[51] Combination chemotherapy is recommended as in other types of LSA, with variable responses reported.

Intranasal Lymphosarcoma

Intranasal LSA generally is seen in FeLV-negative, older cats (median age 8 to 9 years). It usually is B-cell in origin, although epitheliotrophic T-cell LSA[52] also has been reported. Clinical signs associated with intranasal LSA include nasal discharge, dyspnea, epistaxis, stertor, facial deformity, anorexia, epiphora, exophthalmos, and/or sneezing.[53] LSA is a common cause of nasopharyngeal clinical signs. It was diagnosed in 26 of 53 cats with signs of nasopharyngeal disease.[54]

Skull radiographs can be used in the private practice setting to identify a soft tissue density mass within the nasal passages and bony lysis secondary to tumor invasion. An intraoral view is the most useful to eliminate the issues of silhouetting and summation of other soft tissue and bony structures of the skull. A CT scan is most useful to determine the extent of disease, guide intranasal mass biopsy, and plan radiation treatment. Usually, nasal LSA is solitary, but it can be multicentric and necessitate complete systemic staging (see Table 66-1) to determine prognosis and therapy. Aspiration cytology of the mandibular lymph nodes is recommended. If systemic disease is found, chemotherapy must be recommended as the sole therapy or as part of a combined treatment regimen.

The ideal treatment for localized nasal LSA has yet to be determined. Radiation as a solitary therapy in total dosages of 8 to 44 Gy has provided prolonged remissions (12 to 69 months) in some patients.[55,56] Coarsely fractionated therapy has been suggested to be as effective as conventional fractionation in the treatment of nasal LSA.[43] Chemotherapy as a solitary therapy also has been used to treat nasal LSA, with some responses.[44]

Ocular Lymphosarcoma

Ocular LSA may be found as a primary entity, but usually it is found concurrently with systemic disease.[57] Clinical signs include uveitis, anterior chamber or vitreous cellular debris, pupillary abnormalities, glaucoma, retinal infiltration or detachment, third eyelid thickening and prolapse, and possibly exophthalmos if LSA is present in the retrobulbar space (Figure 66-6). Diagnosis is made through enucleation and histopathology, or possibly by fine-needle aspiration cytology of the anterior chamber (see Chapter 3).[43,57]

Treatment may include systemic chemotherapy, topical or subconjunctival injection of corticosteroids, or possibly enucleation to palliate discomfort. Radiation of retrobulbar LSA can achieve remissions and resolve exophthalmos with little risk of radiation effects to the eye, because only a few fractions appear to be necessary to achieve local remission. As with all LSA, systemic chemotherapy should be used in conjunction with any use of radiation therapy.

Renal Lymphosarcoma

Renal LSA is associated with signs of renal failure, including polyuria and polydipsia, weight loss, anorexia, and depression. It usually is found in conjunction with systemic LSA but may

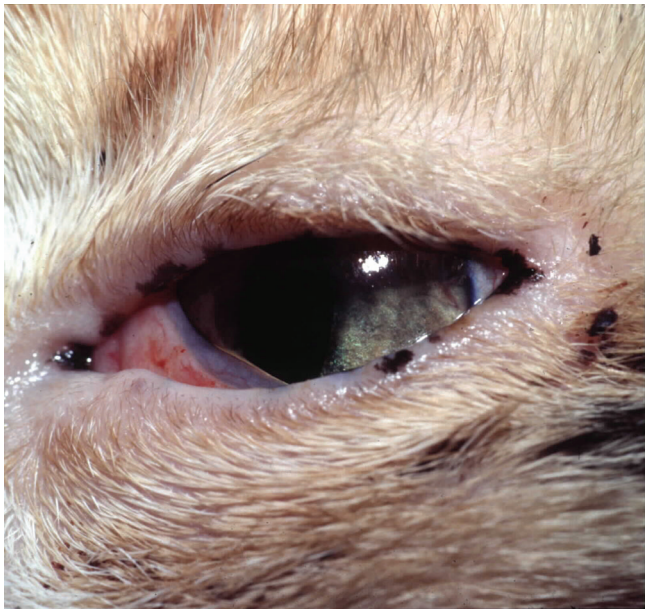

Figure 66-6. This cat with systemic LSA showed signs of ocular involvement, including abnormal pupil shape, uveitis, and conjunctival hyperemia.

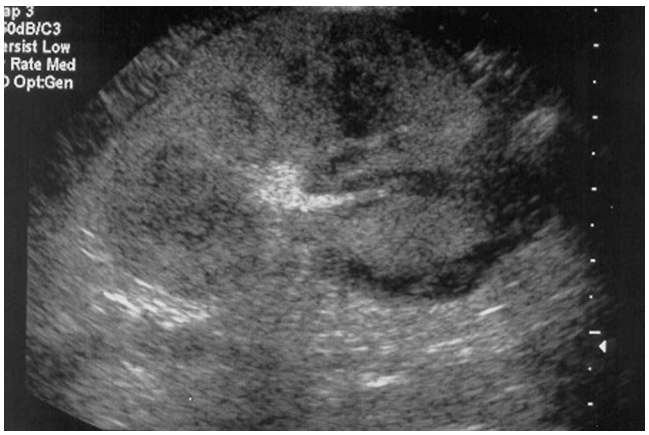

Figure 66-7. Renal lymphosarcoma.

be primary in approximately 33 per cent of cases.[20,58,59] Between 25 and 50 per cent of affected cats are FeLV-positive,[10,58] and renal LSA appears to be primarily B-cell in origin.[10,11] Between 40 and 50 per cent of cats with renal lymphoma have or develop central nervous system involvement (see Chapter 51).[58] Bilateral renomegaly can be palpated on physical examination (Figure 66-7).

Published remission rates with combination chemotherapy protocols range from 16 to 61 per cent.[47,48,58] Median survival times range from 4 to 5 months,[10,47,48] although some cats have survived years. Protocols containing cytosine arabinoside have been recommended because of its potential ability to prevent the CNS relapse seen in cats treated without agents that cross the blood-brain barrier.[58]

Central Nervous System Lymphosarcoma

Central nervous system (CNS) LSA can be separated into intracranial and spinal LSA. Intracranial LSA has been associated with seizures, cranial nerve deficits, ataxia, circling and blindness, anorexia and lethargy, hyperesthesia, aggression, and intention tremors.[60,61] Spinal LSA is associated with neurological signs reflective of the spinal cord segments affected. Symmetrical or asymmetrical paraparesis or tetraparesis or paralysis, hyperesthesia or hypoesthesia, lower motor neuron dysfunction, and peracute onset or rapid progression have been observed (see Chapter 51).[62]

Approximately 70 per cent of cats with spinal LSA have concurrent bone marrow involvement, which may preclude the need for invasive diagnostic evaluation in a cat with paraparesis. The vast majority (84 to 100 per cent) of these cats are FeLV positive.[23,62] Many have other organ system involvement, especially renal (43.5 per cent).[62] Cerebrospinal fluid analysis generally yields nonspecific findings of mixed pleocytosis and elevated protein content, but neoplastic lymphocytes can be seen.[62]

Bony spinal lesions generally are not observed on radiographs; myelograms reveal extradural compressive lesions in approximately 70 per cent of affected cats, although occasional intramedullary lesions or normal myelograms are noted.[62] Other imaging may be necessary, dependent upon clinical signs. Localization and diagnosis of spinal LSA may require a spinal series/myelogram/CT and/or MRI.

Most cats with intracranial LSA have been FeLV negative, and tumors usually are B-cell in origin, although the occasional T-cell LSA has been reported.[60,61,63]

Therapy for CNS LSA includes localized treatment of mass lesions with surgical decompression or radiation therapy. I have performed weekly intrathecal chemotherapy with cytosine arabinoside (100 mg/m^2) with positive results in some cats with lymphoblasts present within the CSF. The CSF usually is cleared of tumor cells within four to five treatments, with resolution of the neurological signs. Concurrent chemotherapy is recommended with any local treatment because of the prevalence of systemic disease. Chemotherapy also may be used as a solitary therapy, although agents that cross the blood-brain barrier (CCNU, cytosine arabinoside) should be included in the protocol for all but extradural lesions. Response to corticosteroids alone in spinal LSA usually is minimal, with duration of remission of 4 to 10 weeks, so combination chemotherapy is preferred.[61] COP-based protocols have resulted in a median remission time of approximately 32 weeks (range, 5 to 62 weeks) in approximately 50 per cent of patients with spinal LSA.[23,48,62,64] The addition of doxorubicin to protocols has been recommended and may provide better results.[43]

Cardiac Lymphosarcoma

Cardiac LSA may be solitary but usually is part of systemic disease, as documented in necropsy studies. Myocardial infiltration may be present in 10 to 20 per cent of cats with LSA, although it rarely causes clinical signs. When clinical signs occur, they are related to pericardial effusion, arrhythmias, and syncope.[65-68] Cardiomegaly may be noted on radiographs, and echocardiography may demonstrate pericardial effusion, mass lesions, and/or diffuse thickening of ventricular walls consistent with infiltrative disease.[65,66,68] Diagnosis usually is indirect, through confirmation of LSA in other organs, because pericardiocentesis rarely yields tumor cells, and myocardial biopsy usually is not pursued.[66,68] Complete staging (see Table 66-1) is recommended to identify other organ involvement for

diagnostic and staging purposes. Remission and survival times for cats with cardiac signs historically have been short (weeks) with prednisone or COP chemotherapy.[65,66]

Laryngeal or Tracheal Lymphosarcoma

Laryngeal or tracheal LSA generally causes signs of dyspnea, including exercise intolerance, wheezing, cyanosis, inspiratory stridor, coughing, and gagging.[69-73] Signs of tracheal or laryngeal disease should prompt cervical radiographs, which may demonstrate a laryngeal or tracheal mass occluding the tracheal lumen. Endoscopy/bronchoscopy can be used to visualize masses and guide biopsies.

As with most forms of LSA, surgical excision alone results in relapse,[71-73] so combination chemotherapy must be recommended. Radiation therapy may be useful as an adjunct to systemic therapy to induce rapid remissions and to relieve clinical signs, and long-term remissions (months to years) can be achieved in some patients with systemic chemotherapy.[69,71]

Cutaneous Lymphosarcoma

Cutaneous LSA is seen primarily in older (10 to 12 years), FeLV-negative cats.[74,75] The disease can present as solitary, erythematous, plaquelike, or nodular lesions, or patients may demonstrate generalized erythema and scaling (Figure 66-8).[17,75-82] The lesions generally are pruritic and may be painful. Over time, the solitary lesions usually are progressive and become more generalized. It may take months to years for patients to be diagnosed, because other more common feline skin diseases are considered and treated first. Diagnosis is confirmed with biopsy of the skin, and lymph node biopsy also should be performed even in the presence of normal-size nodes to differentiate hyperplasia from nodal infiltration of LSA, along with the usual tests for LSA staging (see Table 66-1).

Treatment for localized epitheliotropic T-cell LSA in human beings usually is skin-directed therapy, often total skin electron-beam radiation therapy[83]; this option has not been reported in cats, but I have treated one cat with radiation with resolution of the lesions for several years. With more availability of electron-beam linear accelerators, which reduce or eliminate the risk of internal organ effects from radiation, this option may be used more commonly in veterinary patients. However, as with other forms of LSA, the risk of systemic disease development prompts the recommendation of combination chemotherapy. Corticosteroids alone, either oral or topical, may be palliative in treating pruritus, but remissions usually are not achieved.[76,84] Some reports have shown PR or CR in some lesions with COP protocols, but most were short-lived (weeks to months).[78,79] Doxorubicin should be investigated as a treatment option, as should CCNU, considering its usefulness in treatment of canine cutaneous LSA.[85] Retinoic acid derivatives generally are not recommended for treatment of cats with cutaneous LSA, because no evidence of remission has been seen; however, few affected cats have been described.[81]

A suggested cutaneous paraneoplastic syndrome associated with multicentric LSA has been reported, with cats presenting for symmetric cutaneous necrosis of the hind feet.[86] Sezary syndrome, described in human beings as cutaneous T-cell LSA with concurrent circulating atypical lymphocytes, also has been reported in a cat.[80] Cutaneous LSA has been associated with paraneoplastic monoclonal gammopathy, hyperviscosity, and hypercalcemia.[17]

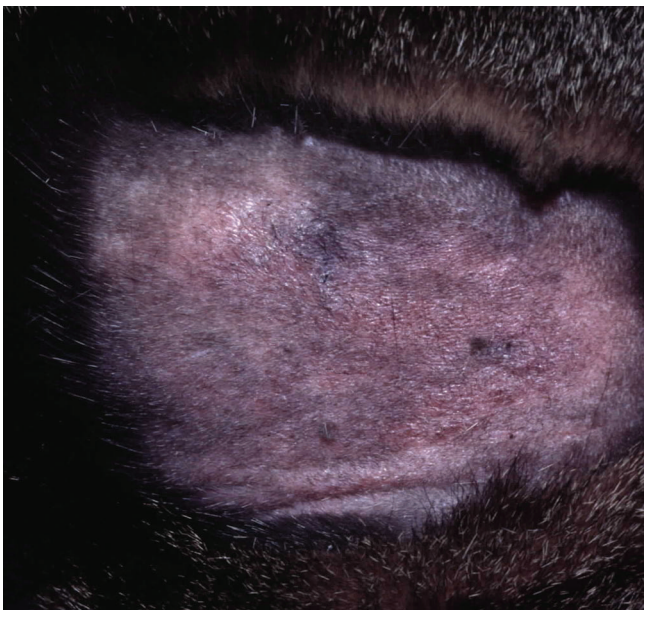

Figure 66-8. This cat with epitheliotropic LSA demonstrates a patch of skin with scaling and erythema.

Bone Lymphosarcoma

Bone LSA has been reported rarely in cats. One case report described bilateral lytic lesions in the tarsi of a FeLV-negative cat,[87] whereas another report described distal radius and ulna lesions in four young, related cats that progressed to systemic disease within 5 months.[88] Local extension of extradural spinal LSA into vertebrae also has been described.[89-92] Treatment of bone LSA has not been reported, but multiagent chemotherapy has been recommended, with or without palliative radiation therapy, for individual bone lesions.[43]

Oral Cavity Lymphosarcoma

Oral cavity LSA has been reported in the gingival,[48] maxillary, and mandibular areas.[56] Weeks to months of response to chemotherapy and radiation therapy as solitary treatments occurred, but the cats relapsed locally or systemically. Perhaps combining radiation and chemotherapy would provide longer remissions and survival, although this remains to be proven.

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Chapter 67

MALIGNANT EFFUSIONS

Elizabeth A. Spangler

Many disease processes, including primary and metastatic neoplasia, can lead to an abnormal accumulation of fluid within the pleural, peritoneal, or pericardial space. Clinical signs vary, depending on the body cavity affected, the rate and magnitude of fluid accumulation, and the nature of the underlying cause for effusion. In some patients, the primary problem is clinically silent, and signs associated with the presence of effusion are the first indication of illness. Fluid analysis is crucial in the diagnostic evaluation of any patient with effusion and can yield insights regarding the etiology, treatment options, and prognosis for recovery. Fluid samples generally can be obtained through methods that are minimally invasive and well tolerated by most patients. Fluid analysis is relatively inexpensive, and the identification of neoplastic cells in an effusion may eliminate the need for more costly and aggressive diagnostic procedures.

MECHANISMS OF EFFUSION

A small volume of fluid normally is present within the pleural, peritoneal, and pericardial spaces to provide lubrication that allows frictionless movement of the organs during normal activity. When healthy, cats have a balance between fluid production and its clearance via the lymphatic system, so large volumes of fluid do not accumulate. This process is driven by a combination of factors, including hydrostatic pressure, colloid osmotic pressure, vascular endothelial permeability, and lymphatic drainage.[1] Neoplasia can disrupt this balance in many ways, resulting in formation of an effusion. For example, venous compression by a mass may cause increased hydrostatic pressure driving fluid production. Obstruction of lymphatic vessels results in decreased fluid clearance and can occur both through extraluminal compression by a mass and intraluminal obstruction by tumor emboli. In addition, the proliferation of neoplastic cells often is accompanied by inflammation with release of vasoactive substances, resulting in increased venous hydrostatic pressure and increased vascular permeability, both of which contribute to effusion. Inflammation also contributes to the cellularity of the effusion, through chemotaxis of inflammatory cells and the proliferation and exfoliation of reactive mesothelial cells. Exfoliation of neoplastic cells is variable but can make a significant contribution to the total nucleated cell population, and cytological examination of the fluid sometimes yields definitive evidence of neoplasia.

CLINICAL PRESENTATION AND SIGNIFICANCE OF EFFUSION

Pleural Effusion

A general discussion of feline pleural effusion was presented in a previous volume of this text.[2] Regardless of the underlying cause, clinical signs associated with pleural effusion typically include dyspnea, tachypnea, shallow respiration, and/or increased inspiratory effort. Heart and lung sounds may be muffled or absent over some areas of the thorax, depending on the distribution of the effusion. Additional physical examination findings sometimes suggest a specific underlying disease process. For example, the presence of a cranial mediastinal mass may be accompanied by decreased thoracic compressibility, caudal displacement of the apex heartbeat, or dysphagia/regurgitation because of compression of the esophagus. In one retrospective study of 82 cats,[3] neoplasia was found to be the underlying cause for pleural effusion in 23 per cent of affected cats; the majority of those cases (14 of 19) had mediastinal lymphoma. Carcinomas (metastatic or primary pulmonary neoplasia) were present in 6 per cent of the cases examined. Cardiovascular disease also was a common cause for pleural effusion and was diagnosed in 13 per cent of the cats. In another study, carcinomas and round cell tumors (lymphoma, mast cell tumor) were detected in approximately equal numbers, with rare sarcomas identified.[4]

Pleural effusion is visualized easily radiographically (Figure 67-1) or through ultrasound examination, but cats with pleural effusion often have a poor tolerance for the stress associated with diagnostic procedures such as radiographs. In contrast, thoracocentesis usually is well tolerated and may provide clinical benefit and material for diagnostic evaluation. Thoracocentesis is performed with the cat either standing or in sternal recumbency and typically requires only moderate restraint. Thoracocentesis is performed at the sixth, seventh, or eighth intercostal space, slightly below the level of the costochondral junction, with a 20-gauge to 22-gauge butterfly catheter

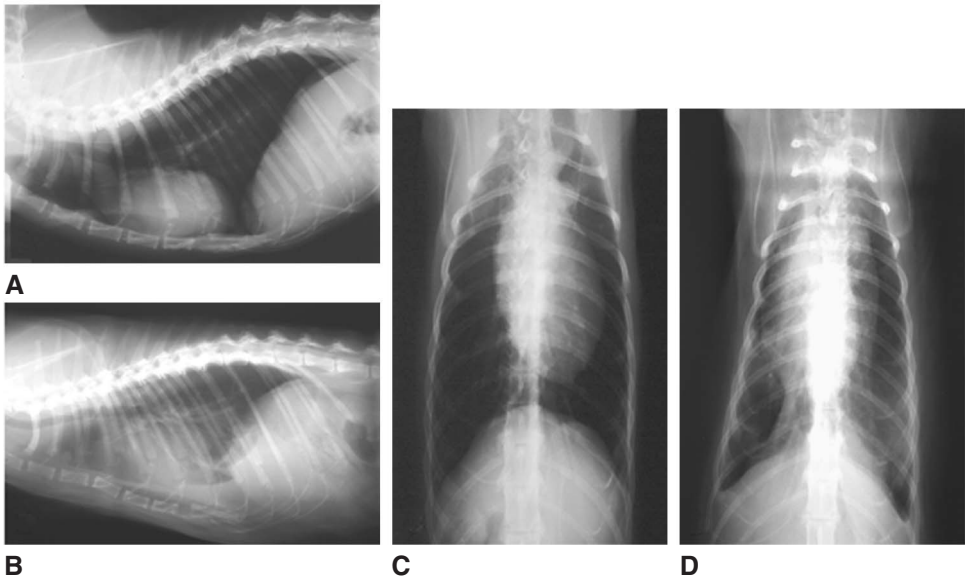

Figure 67-1. **A** through **D,** Lateral and ventrodorsal thoracic radiographs of a cat. **A** and **C,** No pleural effusion is present. **B** and **D,** Taken about 2 years later, these show moderate pleural effusion in the same cat. **B** and **D** show silhouetting of the cardiac shadow by fluid. In the lateral view **(B)** the lung lobes are retracted from the sternum and the caudal lung margins are rounded. In the ventrodorsal view **(D)** the lung lobes are rounded at the costophrenic angles, and the lungs are slightly retracted from the thoracic wall.

attached to a three-way stopcock and syringe. The site for thoracocentesis is clipped and prepared aseptically, and the needle is introduced at the center of the intercostal space to avoid large vessels located at the caudal rib margins.[5] Gentle suction is applied to collect the fluid. The process of fluid analysis is outlined below. Thoracic radiographs performed after removal of the fluid may allow identification of pulmonary or mediastinal masses.

Peritoneal Effusion

Peritoneal effusion is recognized less frequently than pleural effusion in cats, perhaps because small amounts of fluid are not easily detectable on physical examination. Large volumes of fluid may cause evident abdominal distension, and in severe cases, dyspnea can result from cranial displacement of the diaphragm. Abdominal radiographs show a loss of serosal detail but are relatively noninformative. Ultrasound examination is a more sensitive tool for the detection of even small volumes of abdominal effusion and also may reveal the presence of a mass, organomegaly, or lymphadenopathy (Figures 67-2 through 67-4).[6] In some patients, no cause for effusion is evident. If a lesion is detected, it may be in a location difficult to approach by methods short of exploratory laparotomy. In this setting, fluid analysis provides a less invasive avenue to investigate the nature of the underlying disease process. In a retrospective study of cats with peritoneal effusion, cardiovascular disease and neoplasia were found to be the most common underlying disease processes in adult cats.[7] The authors of this study note that the prevalence of dilated cardiomyopathy (DCM) decreased markedly after 1987, when taurine supplementation of commercial pet foods became common, and subsequently, neoplasia was the most frequent cause for peritoneal effusion identified.[7] Specific forms of neoplasia found in this study included carcinoma (7 of 18), lymphoma (5 of 18), sarcoma (4 of 18), and mast cell tumor (2 of 18). In the majority of these cases the fluid was a modified transudate, and neoplastic cells were identified definitively in only 23 per cent of the samples evaluated.

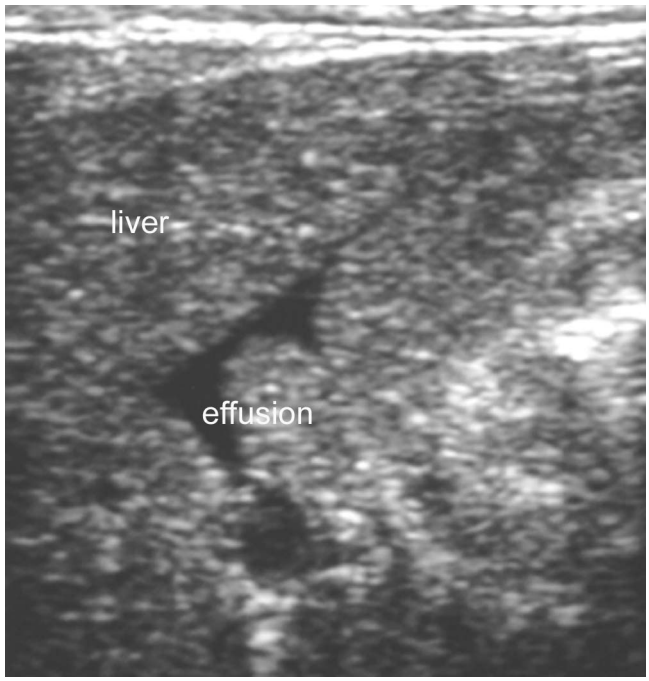

Figure 67-2. Ultrasound image of the liver in a cat with mild abdominal effusion. A small accumulation of anechoic fluid separates the liver lobes.

With the exception of patients that have suffered acute trauma, abdominocentesis can be delayed safely until imaging

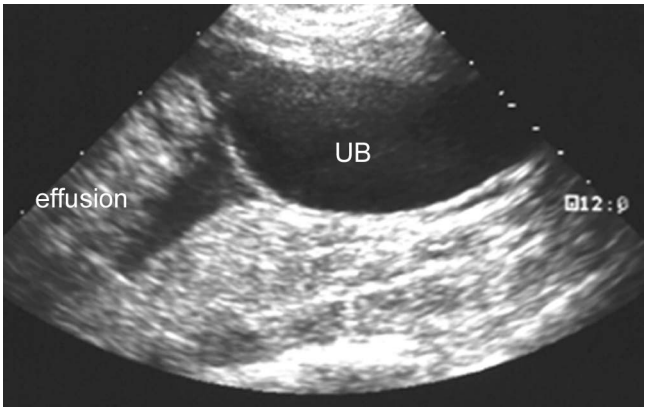

Figure 67-3. Ultrasound image of the urinary bladder in a cat with abdominal effusion. Free fluid within the abdominal cavity is evident near the apex of the urinary bladder. The bladder wall is sharply defined by the presence of fluid on either side.

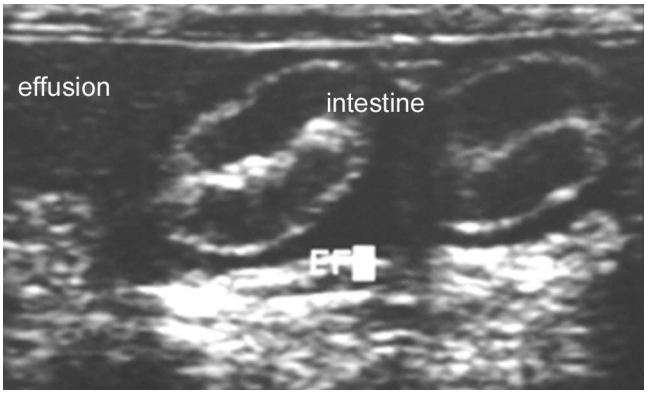

Figure 67-4. Ultrasound image showing a transverse view of segments of the intestine in a cat with abdominal effusion. A moderate accumulation of anechoic fluid separates the intestinal loops.

studies have been performed to verify the presence of an effusion. In cases in which fluid is abundant, a sample usually can be obtained through aspiration on the midline just caudal to the umbilicus, with the patient in lateral recumbency. In patients that have only a small volume of effusion, ultrasound-guided aspiration may be necessary to retrieve a sample. In most feline patients, fluid can be collected with a 20-gauge or 22-gauge butterfly catheter with a syringe attached. As for thoracocentesis, the site of catheter insertion should be clipped and prepared aseptically.[8] A volume of as little as 1 ml of fluid is sufficient for complete evaluation. Rapid removal of large volumes of fluid from the abdomen may result in hypovolemia and is not recommended.

Pericardial Effusion

Pericardial disease is uncommon in cats and often is asymptomatic.[9] Moreover, physical examination findings that typically are present in dogs with pericardial effusion (muffled heart sounds, jugular vein distension, pulsus paradoxus) are seldom evident in cats. Radiographs may reveal generalized cardiomegaly, but echocardiography is the most useful diagnostic tool for identification of feline pericardial effusion. In a large retrospective study evaluating necropsy results for 2852 cats, pericardial effusion was identified in only 2 per cent, and antemortem diagnosis was made in only a small fraction of those cases.[9] Structural heart disease was the most common underlying cause identified (28 per cent; 18 of 66). Metastatic neoplasia resulted in pericardial disease in 18 per cent (12 of 66) of the cases evaluated and was divided equally between lymphoma and various carcinomas.[9] Canine pericardial effusion often is hemorrhagic, compromising the diagnostic value of fluid cytology. In contrast, the authors of the study described above found feline pericardial fluid to have a more varied composition, which suggests that fluid analysis may be an informative test.

Despite this observation, pericardiocentesis is a more involved procedure than collection of pleural or peritoneal fluid, and the risks associated with this process are somewhat greater. Moreover, cardiac tamponade is uncommon in cats; therefore pericardiocentesis rarely is a clinical necessity, and other diagnostic procedures are the preferred option for most patients.

FLUID ANALYSIS

Many sources are available that provide an overview of the process of fluid analysis.[1,10-13] Fluid samples intended for routine evaluation should be placed into EDTA tubes (purple top) to prevent clot formation. Additional samples should be saved in sterile tubes without additives (red top) to allow for biochemical assays or culture. Complete fluid analysis includes an assessment of gross appearance (color, clarity), a determination of the total nucleated cell count (TNCC) and protein content, and microscopic examination. Protein content is measured in the supernatant, after centrifugation of a small volume of fluid, using either a refractometer or an automated analyzer. The TNCC can be determined with a hemacytometer or automated cell counter. Clumped cells or a large amount of particulate debris result in an inaccurate count. Effusions can be classified broadly as transudates, modified transudates, or exudates based on cellularity and protein content; this strategy is outlined in Table 67-1. Such categorization of effusions is helpful in establishing a list of differential diagnoses for the underlying disease process.

Using standard methods of fluid classification, transudates have a low TNCC and protein content (protein <2.5 g/dL; TNCC <1000/μL). Accumulation of a transudate results from changes in hydrostatic and osmotic pressure, whereas vascular permeability remains normal. This type of effusion typically is associated with profound hypoproteinemia that sometimes is accompanied by venous congestion or portal hypertension. The nucleated cells seen in a transudate are predominantly mononuclear (macrophages, mesothelial cells, and small lymphocytes), and a small number of nondegenerate neutrophils may be present.

Modified transudates have a greater nucleated cell count and/or protein content than transudates (protein >2.5 g/dL; TNCC >1000/μL). Formation of a modified transudate usually results from increased venous hydrostatic pressure; a classic example is the fluid that may accumulate in congestive heart failure. In some cases the effusion may have an inflammatory component, which causes an increase in vascular permeability. The majority of the cells present in a modified transudate are

Table 67-1 | **General Guidelines for the Classification of Body Cavity Effusions**

TYPE OF EFFUSION	APPEARANCE	TOTAL NUCLEATED CELL COUNT (CELLS/μL)	PROTEIN CONTENT (g/dL)	CYTOLOGY
Transudate	Clear	<1000	<2.5	Predominantly mononuclear cells (macrophages, reactive mesothelial cells, small lymphocytes)
Modified transudate	Clear to serosanguineous	>1000	>2.5	Predominantly mononuclear cells with a variable number of nondegenerate neutrophils
Exudate	Turbid and/or serosanguineous; may contain aggregates of cells or fibrinous material	>5000	>3.0	Varied; often contains a large proportion of degenerate or nondegenerate neutrophils

still mononuclear, but an increased proportion may be nondegenerate neutrophils.

Formation of an exudate reflects a marked increase in the transmigration of inflammatory cells because of chemotactic stimuli and an increase in vascular permeability. These fluids also have an increased protein content (protein >3 g/dL; TNCC >5000/μL). These events arise most often secondary to the severe inflammation that accompanies a septic process. Neutrophils are the predominant cell type seen in most exudates, and these cells may exhibit marked degenerative change if a septic process is present (see Chapter 61).

An alternative method for classification of feline pleural effusion has been suggested, with guidelines that allow rapid identification of fluids associated with congestive heart failure or bacterial sepsis.[14] Fluid parameters that are evaluated include the differential cell count, lactate dehydrogenase (LDH) activity, pH, and glucose content. With this method, transudates are identified as those fluids with an LDH less than 200 IU/L and are attributed to cardiac disease, hypoproteinemia, or fluid overload. Septic effusions and those associated with malignancy are exudative (LDH >200 IU/L), and these are distinguished further based on pH, glucose content, and neutrophil count. Effusions associated with malignancy typically have a normal to high pH (>7.4), a moderately low glucose content (10 to 80 mg/dL), and a low neutrophil count (<30 per cent of TNCC). In the absence of trauma, a red blood cell count greater than 50,000/μL lends further support to the possibility that the effusion is associated with malignancy. Ultimately, identification of neoplastic cells on microscopic examination of the fluid is still necessary to reach a definitive diagnosis of neoplasia.

The gross appearance of the fluid is informative in cases of hemorrhage or chylous effusion. If the fluid is grossly hemorrhagic, determination of the fluid packed cell volume (PCV) is warranted, but cytological examination is unlikely to be informative. If hemorrhage is longstanding, erythrophagocytosis and/or macrophages containing hemosiderin may be seen. Chylous effusions typically have an opalescent to milky white appearance. They may be classified as modified transudates or exudates based on cellularity. The defining characteristic of a chylous effusion is that the fluid triglyceride content is greater than that of the serum.[15] The differential cell count varies; small lymphocytes predominate acutely, whereas a mixed cell population including neutrophils, lymphocytes, macrophages, and eosinophils may be seen with chronicity. Chylous effusion reflects leakage of fluid from the lymphatic vessels and can arise for varied reasons including trauma and congestive heart failure (see Chapter 40). Chylous effusion has been reported infrequently to accompany neoplasia.[15]

Effusions associated with neoplasia may fall into any of the categories described above. There is disagreement as to whether or not microscopic examination of transudative fluids for detection of neoplastic cells is warranted.[14,16] Although the prediction is that neoplastic cells will be found rarely in a transudate, examination of a sediment or cytospin preparation can be accomplished rapidly and is recommended because it may allow detection of an abnormal cell population that may not be recognized through other methods of fluid analysis.

Microscopic examination of an effusion allows further subclassification based on the cell types present and may reveal a specific etiology in some cases. Several methods exist for preparation of smears from an effusion. Fluids of moderate to high cellularity can be smeared directly with the same technique as for a blood smear. This technique generates a feathered edge where nucleated cells tend to accumulate, and it also produces a monolayer in which differential cell counts can be performed and cell morphology is better preserved. Smears from fluids of low cellularity ideally are made after preparation of a sediment. This involves low-speed centrifugation of the sample (approximately 450 *g* for 5 to 10 minutes) to create a loose pellet of cells; most of the supernatant is removed, the cell pellet is resuspended in a small volume of the remaining fluid, and smears are prepared as described above. Once dry, smears typically are stained with a Romanowsky-type stain (Wright-Giemsa, Diff-Quik).

Cytological identification of neoplasia through fluid analysis requires exfoliation of the neoplastic cells in numbers sufficient for detection. In cases in which neoplastic cells are not readily identified microscopically, additional fluid parameters such as pH or enzyme activity may help to differentiate neoplastic from nonneoplastic disease processes.[14,17,18] Unfortunately, such parameters lack specificity and thus cannot provide the sole basis for diagnosis. In retrospective studies of human and veterinary patients, fluid cytology has shown moderate sensitivity and excellent specificity for the detection of neoplasia.[3,4,7,19,20] One example is the study by Hirschberger, et al,[4] who evaluated cytological detection of neoplasia in canine and feline patients with pleural or peritoneal effusion. For this study, the diagnosis of malignancy was confirmed by histopathological evaluation. Twenty-five per cent of the cats in their study population had neoplasia as the underlying

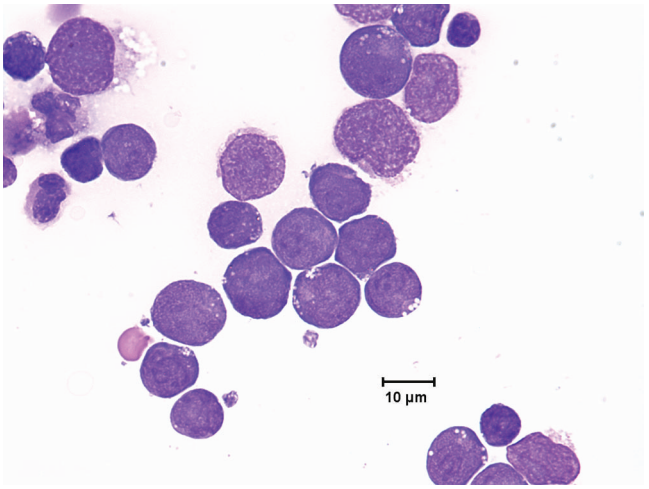

Figure 67-5. Pleural fluid from a cat with mediastinal lymphoma. The majority of the cells present are lymphoblasts, with prominent nucleoli (×600).

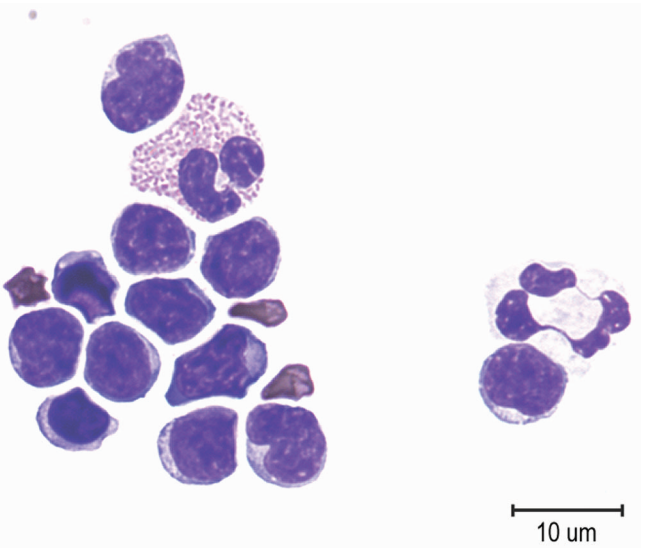

Figure 67-6. Chylous pleural fluid from a cat. The majority of the cells present are small lymphocytes. Occasional nondegenerate neutrophils and eosinophils also are seen (×1000).

disease resulting in effusion. Fifty-six per cent of the tumors were discrete cell neoplasms (mostly lymphoma) and 41 per cent were carcinomas. They found that cytology was 61 per cent sensitive and 100 per cent specific for detection of neoplasia overall (positive predictive value 100 per cent; negative predictive value 90 per cent). These authors noted that cytology was more effective in the identification of round cell tumors than for carcinomas or sarcomas. Similarly, another group of investigators concluded that based on fluid cytology, only lymphoma was identified consistently when several independent pathologists reviewed smears.[21]

The sensitivity and specificity of cytological evaluation ultimately depend on the skill and degree of caution employed by the pathologist. Thus there may be significant variation in the fluid assessment made by different evaluators. With this caution in mind, specific cytological characteristics can be applied in the diagnosis of various forms of neoplasia. Several examples are discussed below.

EFFUSIONS ASSOCIATED WITH SPECIFIC FORMS OF NEOPLASIA

Lymphoma and Thymoma

Effusion resulting from lymphoma is the form of malignant effusion identified most readily on cytology (Figure 67-5). The fluid tends to be highly cellular, and in most cases, the majority of the nucleated cells present are lymphoblasts. Historically, mediastinal lymphoma with accompanying pleural effusion was seen commonly in feline patients. This form of lymphoma occurs most often in young cats (<5 years old), and the majority are feline leukemia virus (FeLV) positive. In recent years, mediastinal lymphoma has become less prevalent, although the bias for young cats with FeLV infection is still observed.[22]

Effusion with a predominance of small lymphocytes presents a greater diagnostic challenge (Figure 67-6). Such an effusion can occur with small cell lymphoma but also may arise in cats with chylothorax, lymphoplasmacytic inflammation, or thymoma. If lymphoma is strongly suspected, additional diagnostic tests should be performed to diagnose lymphoma definitively. For example, immunocytochemistry can be used to determine the cell lineage (B cell vs. T cell).[23] Flow cytometry allows assessment of DNA ploidy. In the future, PCR may allow examination of immunoglobulin gene or T-cell receptor gene rearrangement to assess clonality of the lymphocyte population,[24] although this technique is not yet generally available for feline patients.

When effusion is associated with thymoma, the fluid typically contains many small lymphocytes accompanied by a variable number of eosinophils and mast cells. Occasionally, epithelial cells from the thymus also may be recognized, and in some cases these may show convincing characteristics of malignancy. Aspiration cytology or biopsy of a mediastinal mass often is necessary to confirm the diagnosis.[25]

Mast Cell Tumor

Visceral mast cell tumor involves the spleen, liver, or intestine most commonly and sometimes is accompanied by an effusion.[26,27] This fluid simply may be reactive, with fluid analysis showing only a modified transudate and no mast cells evident. When neoplastic cells are present in the fluid, they usually are abundant, and their appearance is similar to that of mast cells found at other locations. The cells have a round nucleus placed centrally within a moderate amount of cytoplasm. A variable number of dark purple–staining cytoplasmic granules are seen typically. If staining of mast cell granules with Diff-Quik is equivocal, their presence may be demonstrated more readily through new methylene blue or Giemsa staining. Small numbers of mast cells also may be present in effusion associated with a variety of inflammatory disease processes, and this should not be confused with definitive evidence of neoplasia.

Carcinoma

Carcinomas sometimes are associated with effusion, most often when diffuse metastatic disease is present. Primary tumor sites

that are associated commonly with metastatic disease include lung, mammary gland, pancreas, and transitional epithelium of the urinary bladder. When an effusion is present, large numbers of neoplastic cells often are present in the fluid, and they tend to form variably sized cohesive clusters of cells. Moderate to marked cytological characteristics of malignancy may be evident (Table 67-2; Figure 67-7). Often a mild, mixed inflammatory response also occurs. Differentiation between neoplastic epithelial cells and reactive mesothelial cells in fluid samples is difficult and can present a diagnostic dilemma. Reactive mesothelial cells are pleomorphic in appearance and may exhibit many cytological characteristics suggestive of neoplasia, including anisokaryosis, mitotic figures, and binucleation.[13,19,20,28] As a result, the appearance of these cells sometimes is indistinguishable from that of carcinoma cells (Figure 67-8). This is particularly true if substantial inflammation is present to drive mesothelial reactivity. For this reason, the diagnosis of carcinoma through fluid analysis should be made cautiously and should not be based solely on cytology if marked inflammation is present.

SUMMARY

Diseases that result in the formation of a body cavity effusion often present a diagnostic challenge, and neoplasia is a frequent cause for effusion in cats. Cytological evaluation can be an efficient and cost-effective diagnostic tool when neoplastic cells are identified in the fluid, although this method does have certain limitations. It is crucial to differentiate reactive mesothelial cells from neoplastic cells and this distinction is not always clear. Neoplastic cells are not always exfoliated readily into an effusion, and the absence of those cells on cytological examination does not exclude the possibility of neoplasia as the cause of the effusion. A variety of adjunctive tests are applied to the analysis of effusion samples from human patients, including measurement of specific enzyme activity, immunocytochemistry, and PCR amplification to detect gene rearrangement or expression of a particular gene product.[20,21] In the future, application of such methods to the evaluation of effusions in cats may increase the usefulness of fluid analysis and further limit the need for more invasive diagnostic procedures.

Table 67-2 | **Cytological Features Used to Identify Malignant Cells**

Variation in cell size (anisocytosis)
Variation in nuclear size (anisokaryosis)
High and/or variable nuclear-to-cytoplasmic ratios
Prominent nucleoli that vary in shape and number
Multinucleation
Nuclear molding
Increased mitotic activity
Abnormal mitotic figures

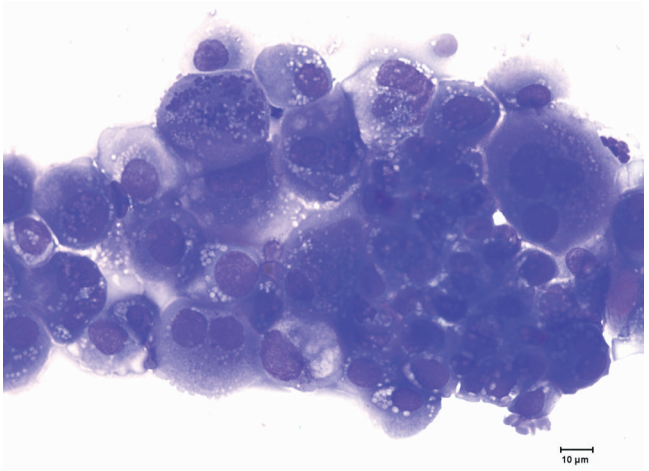

Figure 67-7. A large cluster of carcinoma cells in pleural fluid from a cat characterized by marked anisocytosis and anisokaryosis. Many binucleated and multinucleated cells are present, and occasional mitotic figures are seen (×600).

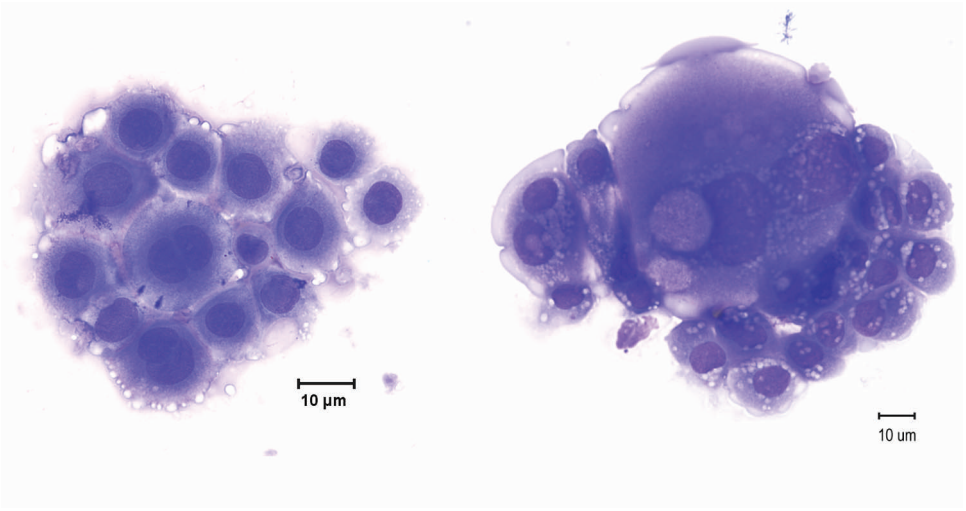

Figure 67-8. A, Group of reactive mesothelial cells in pleural fluid from a cat. Moderate anisocytosis and anisokaryosis and occasional binucleated cells are seen. **B,** Cluster of carcinoma cells exhibiting marked anisocytosis and anisokaryosis (×600).

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Chapter 68

TUMORS OF THE URINARY TRACT

S. Dru Forrester

Tumors may affect any part of the urogenital system (e.g., kidneys, ureters, urinary bladder, urethra, prostate gland); however, most often they occur in the kidneys and urinary bladder in cats.[1-19] Urinary tract neoplasia is rare in cats compared with tumors that involve other sites in the body. In a study of 395 feline tumors, only 1 per cent involved the urinary tract compared with 26 per cent, 21 per cent, and 20 per cent that affected the hemolymphatic, integumentary, and gastrointestinal systems, respectively.[20] Three primary renal tumors were identified, and no cats had lower urinary tract neoplasms in this study.[20]

URINARY BLADDER AND URETHRAL TUMORS

A variety of urinary bladder and urethral tumors have been reported in cats (Table 68-1).* Epithelial tumors are most common and represent 80 per cent of feline urinary bladder tumors. Transitional cell carcinoma (TCC) is the most common histological type and affects 60 per cent of reported cases. Compared with urinary bladder tumors, urethral tumors are rare; only two cases have been reported (one TCC and one leiomyoma).[2,16]

Etiology

Although little is known about the cause of lower urinary tract neoplasia in cats, it is thought to be multifactorial in dogs. Potential risk factors in dogs include female gender, obesity, chronic cystitis associated with administration of cyclophosphamide, and exposure to topical insecticides for flea and tick control, marshes that have been sprayed for mosquito control, and lawns or gardens treated with phenoxy herbicides.[21-25] Carcinogenic substances or metabolites are concentrated and excreted in urine. Because the urinary bladder is a storage reservoir, prolonged exposure of urinary bladder epithelium to carcinogenic substances may explain why urinary bladder tumors are more common than urethral tumors.[12]

Urinary bladder and urethral tumors are rare in cats compared with dogs; therefore cats inherently may be less susceptible to developing lower urinary tract neoplasia. Endogenous carcinogens (e.g., orthoaminophenols) may be produced secondary to metabolism of tryptophan and excreted in urine. Feline urine does not contain tryptophan metabolites, which may explain the decreased occurrence of lower urinary tract neoplasia in cats.[12,26]

Epidemiology

Lower urinary tract neoplasia is most common in older cats.* Although the youngest reported cat was 4 months old (a kitten with benign papilloma), mean ages in several studies have ranged from 9.2 to 13 years.[6,7,12,14,19] In a recent study of epidemiological risk factors for lower urinary tract diseases in cats, those that were 10 to less than 15 years of age were 6.1 times (95 per cent confidence interval [CI] = 3.9, 9.6) more likely to have lower urinary tract neoplasia compared with cats less than 10 years of age; cats more than 15 years of age were 19.4 times (95 per cent CI = 12.3, 30.5) more likely to have neoplasia.[27]

Although no breed predisposition has been documented for lower urinary tract neoplasia in cats, an association may exist between gender (neutered versus intact) and occurrence of neoplasia.[6,7,14,27] More affected females were found in one study (11 of 16 cats) and more affected males in another report (20 of 27 cats); however, statistical comparisons were not made with the hospital population.[7,14] Recently, however, a much larger study including 78 cats with lower urinary tract neoplasia revealed a

*References 1,3-7,12,14,15,17,19.

*References 3,4,6,7,12,14,15,17,19.

Table 68-1 | **Urinary Bladder Tumors Reported in 94 Cats***

TUMOR TYPE	NUMBER OF CATS
EPITHELIAL	
Malignant	
Transitional cell carcinoma	56
Squamous cell carcinoma	6
Adenocarcinoma	4
Papillomatous carcinoma	1
Undifferentiated carcinoma	5
Benign	
Cystadenoma	1
Papilloma	2
MESENCHYMAL	
Malignant	
Leiomyosarcoma	7
Hemangiosarcoma	2
Rhabdomyosarcoma	1
Myxosarcoma	1
Benign	
Leiomyoma	5
Hemangioma	1
Fibroma	1
ROUND CELL	
Lymphoma	2

*References 1,3-7,12,14,15,17,19.

slightly increased risk for spayed females (2.1 times greater, 95 per cent CI = 1.3, 3.2) and castrated males (2.5 times greater, 95 per cent CI = 1.6, 3.9) and reduced risk of neoplasia for sexually intact females (odds ratio = 0.22, 95 per cent CI = 0.09, 0.53).[27]

Pathogenesis

Urinary tract tumors usually are locally invasive and interfere with normal urethral and/or urinary bladder function. Initially, disruption and inflammation of urinary bladder or urethral mucosa cause irritation and signs typical of cystitis. Masses located in the trigone of the urinary bladder may obstruct urine flow from the ureters and cause secondary hydroureter and hydronephrosis, or through the urethra, leading to urethral obstruction.[14,16] Most lower urinary tract tumors are malignant and therefore may metastasize to distant sites (draining lymph nodes, abdominal organs, lungs) and cause clinical signs related to the organ affected (e.g., abdominal effusion, respiratory distress).

Clinical Signs

Clinical signs in cats with urinary bladder or urethral neoplasia may be nonspecific (e.g., lethargy, inappetence, weight loss, vomiting) or suggest lower urinary tract disease.[2,3,6,14-17] Hematuria, stranguria, dysuria, and/or pollakiuria were present in 24 of 27 cats (89 per cent) in one study; hematuria was the most common presenting complaint, observed in 85 per cent of affected cats.[14]

Tenesmus, urethral hemorrhage, blood clots in urine, anuria, and urinary incontinence also may be noted.[4,6,14,16] The average duration of clinical signs before diagnosis in one study was 5 weeks; however, signs may be present for months before diagnostic evaluation is performed.[6,14,15] Finally, urinary bladder tumors may be an incidental finding with no associated clinical signs in a few patients.[6,14]

Physical examination may be normal or may reveal findings consistent with lower urinary tract neoplasia. The most common abnormalities are a palpably thickened urinary bladder and presence of a caudal abdominal mass.[4-6,15] A distended urinary bladder may result from urinary obstruction.[16]

Differential Diagnosis

Most cats with lower urinary tract disease have similar clinical signs, regardless of the underlying cause. Interstitial cystitis is present in approximately two thirds of cats with signs of lower urinary tract disease, whereas neoplasia is diagnosed in less than 2 per cent.[27-29] Other disorders that should be considered in cats with hematuria, pollakiuria, or stranguria include urolithiasis, urethral plugs, urethral strictures, and urinary tract infection.[27-29] Cats with urinary bladder neoplasia may have concomitant lower urinary tract disorders including urolithiasis and urinary tract infection.[6,14,28] Therefore a thorough diagnostic evaluation should be performed in cats at risk for neoplasia (e.g., less than 10 years of age or with persistent hematuria), even when another lower urinary tract disease has been documented.[30]

Diagnosis

Laboratory Evaluation

Routine laboratory tests should include complete blood count, serum chemistries, and urinalysis. Anemia and azotemia (prerenal, renal, and postrenal) are the most common abnormalities identified.[5,14,15] Extreme eosinophilia (>40,000/µl) was associated with TCC of the urinary bladder in one cat.[15] Hematuria is the most common abnormality identified by urinalysis; other findings may include pyuria, proteinuria, and bacteriuria.[3,5,6,14] Neoplastic cells are identified infrequently on urine sediment examination in cats with urinary bladder neoplasia (Figure 68-1).[3,6] Their presence should be interpreted carefully because inflammation can cause epithelial dysplasia, which appears similar cytologically to malignancy.[31] Urine culture should be done in cats with pyuria, bacteriuria, or urinary bladder neoplasia. Urinary tract infection (UTI) was identified in 8 of 14 cats (57 per cent) with urinary bladder neoplasia in one study.[14] Neoplasia may alter host defenses and predispose to UTI; however, other factors probably are involved because UTI has been reported in 46 per cent of cats older than 10 years of age.[32]

Diagnostic Imaging

Diagnostic imaging studies are useful for evaluation of cats with suspected urinary tract neoplasia.[3,6,14,33,34] Survey abdominal radiographs may reveal findings consistent with primary neoplasia (e.g., urinary bladder mass), metastasis (e.g., enlarged sublumbar lymph nodes, osteolytic or proliferative lesions of the pelvis or vertebral bodies), or concomitant diseases (e.g., urolithiasis). I recommend abdominal ultrasound in all older cats with signs of lower urinary tract disorders, even if abdominal radiographs are normal. Ultrasonography may reveal the presence of a urinary bladder mass (Figure 68-2), sublumbar lymphadenopathy, or evidence of hydroureter or

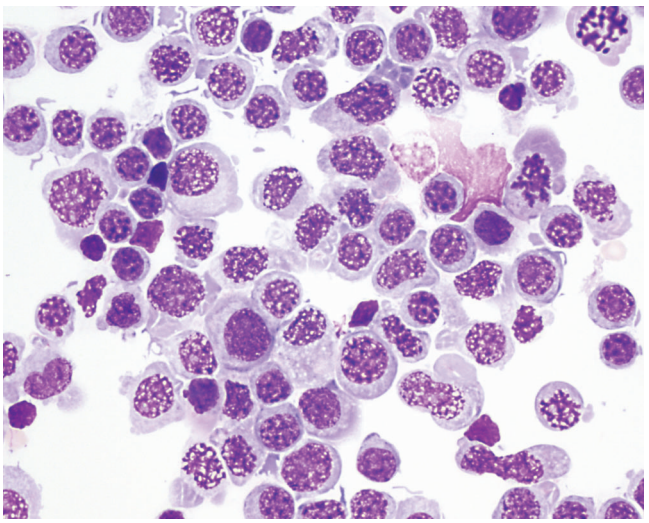

Figure 68-1. Examination of urine sediment from a cat with lower urinary tract neoplasia. Note the presence of numerous transitional epithelial cells (Wright's stain, original magnification 100×). (Courtesy Lois Roth-Johnson, IDEXX Reference Laboratories, North Grafton, MA.)

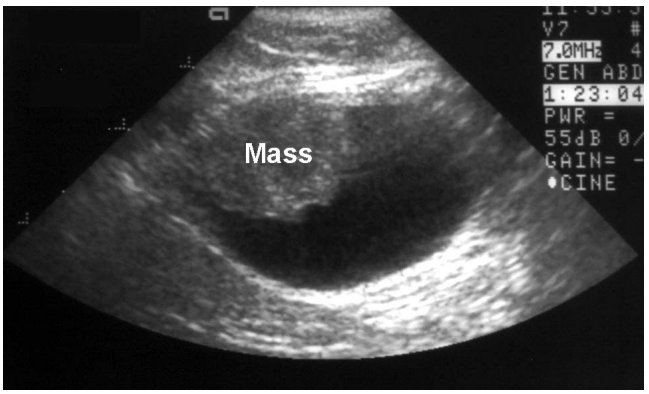

Figure 68-2. Sagittal plane urinary bladder sonogram of a 16-year-old domestic shorthair cat presented for evaluation of chronic kidney disease. The cat had been treated for episodes of urinary tract infection during the past 10 months but did not have clinical signs of lower urinary tract disease. Note the presence of a hyperechoic mass located in the apex of the urinary bladder.

hydronephrosis secondary to urinary obstruction by masses at the urinary bladder trigone. If plain abdominal radiographs or ultrasound fail to demonstrate an abnormality, contrast radiographic procedures (cystography and urethrography) are indicated. Contrast radiography of patients with lower urinary tract neoplasia usually reveals a space-occupying mass in the urinary bladder or urethra.

Microscopic Examination of Tissue

Collection of tissue for microscopic examination is needed to confirm a diagnosis of neoplasia. Samples for cytological evaluation can be obtained easily in most cases, and results may yield a diagnosis when numerous criteria of malignancy are present (Figure 68-3).[17,31,35] However, results of cytological evaluation always must be interpreted carefully along with other diagnostic findings, particularly the presence of urinary tract inflammation. Histological examination is preferred when

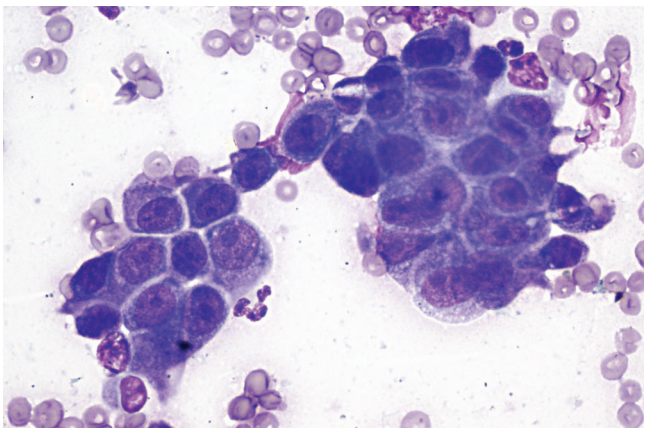

Figure 68-3. Cytological evaluation of a urethral mass in a cat. Note the presence of transitional epithelial cells with numerous characteristics of malignancy; these findings are consistent with transitional cell carcinoma (Wright's stain, original magnification 100×). (Courtesy Lois Roth-Johnson, IDEXX Reference Laboratories, North Grafton, MA.)

cytological findings are equivocal or when more accurate information would alter treatment or the ability to give prognostic information to owners.

Tissue specimens for cytological and histological evaluation may be collected by percutaneous aspiration, catheter-assisted biopsy, uroendoscopy, or open biopsy during surgery.[34,36-40] I have used ultrasound-guided percutaneous aspiration most often to obtain samples from urinary bladder masses without complication.[17,34] However, some authors recommend that percutaneous aspiration procedures, including cystocentesis, be avoided in patients with suspected TCC because of potential for tumor seeding of the needle tract.[41-43] Catheter-assisted biopsy may be an alternative procedure for cats with mucosal lesions of the urinary bladder or urethra.[44] Ultrasound guidance has been used in dogs to facilitate accurate placement of the catheter and enhance diagnostic yield; it seems likely that this also would be helpful in cats.[45] Exploratory celiotomy should be considered if less invasive tests fail to yield a diagnosis, especially if the owner is willing to pursue surgical treatment. Advantages of surgery are that it allows visual inspection of draining lymph nodes and serosal surfaces of the urinary bladder in addition to collection of full-thickness biopsies from the tumor and draining lymph nodes.

Clinical Staging

Determining extent of local tumor invasion and whether regional lymph node involvement or distant metastasis (i.e., clinical staging) occurred provides useful prognostic information and helps guide treatment decisions. As discussed previously, diagnostic imaging of the abdomen is useful for evaluating tumor location, size, and invasiveness, in addition to evidence of metastasis (e.g., sublumbar lymphadenopathy, osteolysis or osteoproliferation of lumbar vertebral bodies or pelvis). Thoracic radiographs also are indicated to detect evidence of metastatic disease (Figure 68-4). Although studies have not been conducted to determine the effect of clinical stage on prognosis in feline lower urinary tract neoplasia, cats with invasive tumors or metastases probably have a less favorable outcome than cats with localized disease.

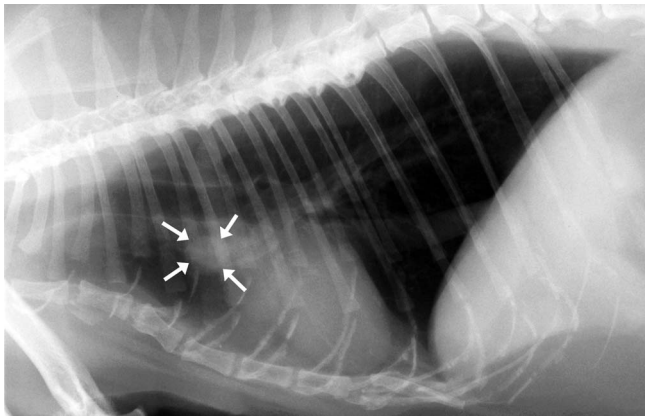

Figure 68-4. Lateral thoracic radiograph of cat in Figure 68-2, taken 3 months after original diagnostic evaluation and surgical removal of the mass. Note the presence of a 1-cm nodule cranial to the heart *(white arrows)*. On the ventrodorsal view (not shown), this density appeared to be present in the left cranial lung lobe. Pulmonary metastasis from the urinary bladder mass was suspected. No evidence existed of a urinary bladder mass on sonographic evaluation of the abdomen.

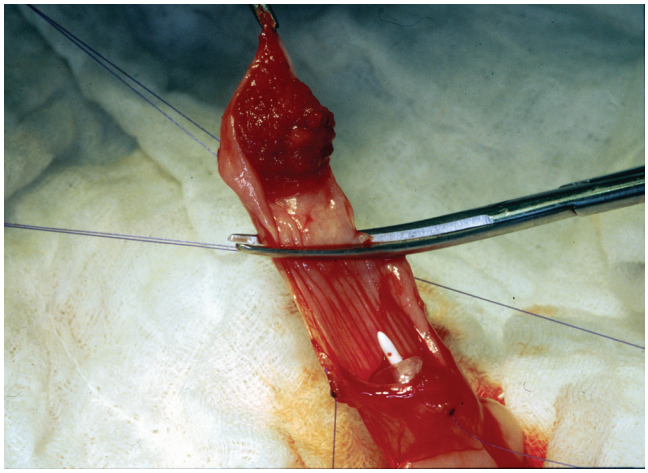

Figure 68-5. Surgery was performed to remove the apical urinary bladder mass and an abdominal lymph node from the cat in Figure 68-2. Histological evaluation of the mass was diagnostic for transitional cell carcinoma; no evidence existed of metastatic disease in the lymph node. Clinical signs of pollakiuria and hematuria recurred 10 to 12 months after surgery; abdominal ultrasonography revealed a large mass in the urinary bladder, consistent with tumor recurrence. (Courtesy Don Waldron, Blacksburg, Virginia.)

Treatment

The most effective method of treating urinary bladder or urethral neoplasia in cats is unknown.[46] General goals of treatment are to remove or decrease size of the primary tumor, control metastatic disease, and alleviate clinical signs of patient discomfort.[46] Unfortunately, in most cases, the disease is advanced by the time of diagnosis, which makes response to treatment less favorable. This may be due, in part, to delayed diagnosis while symptomatic treatment for lower urinary tract disease is administered in cats assumed to have more common disorders such as interstitial cystitis and urolithiasis.

At present, partial cystectomy is considered the treatment of choice for tumors located in the apex or body of the urinary bladder.[46,47] The best prognosis and chance for cure is associated with surgical excision of benign tumors.[14] Removal of malignant tumors may prolong survival time or improve quality of life for a short period (2 to 6 months); however, local recurrence or metastasis is highly likely, even when excision appears complete (Figure 68-5).[14,46] Local implantation of tumor cells in the surgical site (abdominal cavity, incision line) has been associated with manipulation of malignant tumors, primarily those of epithelial origin.[42] Therefore efforts should be made to avoid this complication by isolating the urinary bladder from the abdominal cavity and by changing gloves and instruments after excision of the tumor.[46] Tumors located at the trigone or neck of the urinary bladder cannot be removed without significant complications, including urinary incontinence, and presently no ideal method of urinary diversion that would allow complete cystectomy exists for veterinary patients.[46]

Because of the high rate of recurrence after surgical excision and likelihood of metastasis, systemic treatment should be considered for cats with malignant urinary bladder or urethral tumors. The ideal medical management for cats is unknown; therefore consultation with a veterinary oncologist is indicated. A variety of chemotherapeutic agents (cisplatin, carboplatin, doxorubicin, mitoxantrone, piroxicam) have been administered to dogs with TCC.[48] Cisplatin causes a dose-dependent pulmonary toxicosis in cats and should not be used.[49] Carboplatin, doxorubicin, and mitoxantrone may be used in cats; however, their efficacy for treatment of TCC has not been evaluated in this species. Piroxicam, a nonsteroidal antiinflammatory drug with antitumor activity, has been used alone or in combination with other chemotherapy drugs for managing dogs with TCC.[48] This treatment has been associated with clinical improvement and some partial remissions. I am aware of one cat with TCC and chronic kidney disease that has been treated with piroxicam; side effects were not noted and clinical signs (pollakiuria, hematuria) appeared to improve. The currently recommended dosage for dogs is 0.3 mg/kg PO q24h. Because of tablet size, piroxicam must be reformulated for administration to cats. Potential side effects include gastrointestinal ulceration and nephrotoxicosis.

Management

Management of conditions associated with lower urinary tract neoplasia may be needed to improve quality of life. Urinary tract infections should be treated by administration of an appropriate antimicrobial based on results of culture and susceptibility (see Chapter 48). Urethral obstruction may occur in cats with urethral tumors or urinary bladder tumors that invade the trigone or neck; permanent tube cystostomy should be considered in these cases.[47,50]

Pathological Findings

Although a small number of feline urinary bladder tumors are benign, the overwhelming majority (90 per cent) are malignant and locally invasive (see Table 68-1). In contrast to dogs, urinary bladder tumors in cats often are located at sites other than the trigone. In a report of 17 cats with urinary bladder neoplasia, tumors were found in the fundus (10 cats), dorsal wall (four cats), ventrolateral wall (one cat), trigone (one cat), or diffusely throughout the urinary bladder (one cat).[6] In another

study of 23 cats, tumors were located diffusely (seven cats) or in the ventral floor (six cats), trigone (five cats), or apex (five cats) of the urinary bladder.[14] Metastatic disease has been reported in 26 to 36 per cent of cats with malignant epithelial tumors.[6,14] Most commonly reported sites for metastases include iliac and mesenteric lymph nodes, lungs, and abdominal organs, including the stomach, small intestine, spleen, liver, diaphragm, omentum, and uterine stump.[6,14,15,19]

RENAL TUMORS

The most common tumor affecting the kidneys of cats is lymphoma.[10,51] Lymphoma probably is not a primary renal tumor but instead a systemic disease that involves the kidneys. An Australian study of 118 cats with lymphoma revealed that 36 cats (31 per cent) had renal involvement; six cats had disease restricted to the kidneys alone, 13 had disease of other intraabdominal organs (primarily mesenteric lymph nodes and/or intestines), and 17 had involvement of nonabdominal tissues.[51] The diagnosis of renal involvement was based primarily on physical findings at presentation; it appeared as if cytological or histological evaluation of renal tissue was not done in all cats with renal involvement to confirm the diagnosis.[51] In two other studies, one from the Netherlands and one from the United States, only 3.3 per cent and 6.9 per cent, respectively, of cats with lymphoma had renal involvement. Whether concurrent renal involvement was associated with other anatomical forms was not noted.[52,53]

Primary renal neoplasia is uncommon in cats compared with renal lymphoma. Individual cases have been described in the literature and three reports exist that describe groups of cats with primary renal tumors (Table 68-2).[6,7,9] Epithelial tumors are most common. They represent 70 per cent of feline renal tumors. The remaining 30 per cent of tumors are of connective tissue origin or mixed (nephroblastoma).[6,7,9]

Etiology

The cause of primary renal tumors in cats is unknown. However, lymphoma has been associated with viral infections and environmental factors.[54-56] In one study, 50 per cent of cats with renal lymphoma were positive for infection with feline leukemia virus (FeLV).[10] Although FeLV infection may cause lymphoma in some cats, other factors probably are involved. In a study of Australian cats with lymphoma, 50 per cent were positive for feline immunodeficiency virus (FIV) antibodies.[54]

Table 68-2 | **Primary Renal Tumors Reported in 81 Cats***

TUMOR TYPE	NUMBER OF CATS
EPITHELIAL	
Carcinoma	36
Transitional cell carcinoma	14
Squamous cell carcinoma	3
Adenoma	4
MESENCHYMAL/MIXED	
Nephroblastoma	11
Sarcoma	10
Leiomyosarcoma	2
Hemangiosarcoma	1

*References 6,7,9.

Cats with FIV infection also are at increased risk for lymphoma.[54,56] Recently, the presence of environmental tobacco smoke was reported to be a potential risk factor and cause for lymphoma in cats; the risk increased with both quantity and duration of exposure to passive cigarette smoke.[55]

Epidemiology

No breed or gender predispositions exist for primary renal tumors; however, most cats are older. The mean or median ages of cats with primary renal tumors in three studies ranged from 7 to 11 years; cats ranged in age from 1.5 to 22 years.[6,7,9] The reported mean or median ages of cats with renal lymphoma were 7 and 8.25 years; ages of cats ranged from 1.25 to 17.7 years.[10,51] In one study of cats with lymphoma, males and Siamese and Oriental cats were overrepresented; results of statistical evaluation for gender or breed predispositions within groups based on anatomical location (e.g., cats with renal lymphoma) were not reported.[51]

Pathogenesis

Consequences of renal neoplasia depend on location of tumor within the kidney, whether one or both kidneys are affected, and whether the tumor is benign or malignant. Compared with benign tumors, malignant tumors are more likely to cause destruction of surrounding renal tissue because of their invasive behavior.[7,9] Primary renal tumors almost always involve one kidney, therefore renal failure is unlikely unless concomitant disease of the contralateral kidney exists.[6,9] In contrast, renal lymphoma usually involves both kidneys and neoplastic infiltration of the renal parenchyma may lead to chronic renal failure.[10,57]

Clinical Signs

Cats with renal tumors most often have vague clinical signs, although some cats are asymptomatic.[6,9] Nonspecific findings in cats with primary renal tumors include lethargy, inappetence, weight loss, and vomiting; other signs include hematuria and abdominal distention or pain.[6,9] Physical examination may reveal an enlarged kidney or presence of a mass associated with a kidney. Cats with renal lymphoma often have signs of chronic kidney disease (e.g., polyuria, polydipsia, inappetence, vomiting) and abdominal enlargement. Physical examination often reveals a thin cat with bilateral renomegaly.

Differential Diagnosis

In addition to renal neoplasia, other causes of renomegaly should be considered in cats (Table 68-3).[58] Determination of whether one or both kidneys are enlarged is helpful, because certain disorders are more likely to be characterized by either unilateral or bilateral renomegaly.

Diagnosis

Laboratory Evaluation

Routine laboratory tests including complete blood count, serum chemistries, and urinalysis usually reveal nonspecific findings. Anemia, most likely secondary to chronic inflammation or kidney disease, is the most common abnormality on complete

Table 68-3 | **Disorders Associated with Renomegaly in Cats**

BILATERAL RENOMEGALY
Acromegaly
Renal lymphoma
Primary renal tumors*
Feline infectious peritonitis
Toxic nephropathy (e.g., ethylene glycol)
Polycystic kidneys
Hydronephrosis
Pyelonephritis
Perinephric pseudocysts*
UNILATERAL RENOMEGALY
Primary renal tumors
Renal lymphoma†
Renal compensatory hypertrophy
Perinephric pseudocysts
Hydronephrosis
Pyelonephritis

*Usually unilateral, rarely bilateral.
†Usually bilateral disease, even if only one kidney appears enlarged.

blood count.[9,10] Polycythemia was reported in one cat with a primary renal carcinoma.[9] Leukocytosis also may be present.[10] Azotemia is the most common abnormality on serum chemistries; it may be prerenal or secondary to chronic kidney disease.[9,10,57] Proteinuria may occur in cats with primary renal tumors or renal lymphoma; however, hematuria is the most common finding on urinalysis from cats with primary renal tumors.[9,10]

Diagnostic Imaging

Imaging studies are indicated to detect signs of renal neoplasia and help determine clinical stage. Survey abdominal radiographs may reveal a renal mass or enlarged kidney(s) and are helpful for distinguishing between unilateral and bilateral renomegaly (Figure 68-6).

Abdominal ultrasound provides information about renal size, shape, internal architecture, location, and surrounding structures in the abdominal cavity (Figure 68-7).[33] It may be used to identify diffuse or focal abnormalities of the renal parenchyma, detect renal masses or nodules, and distinguish between solid and focal lesions.[33] Renal lymphoma may be characterized by a multifocal, hyperechoic pattern, or presence of multifocal or diffuse hypoechoic nodules.[59] Excretory urography is used less often for evaluating cats with renomegaly because other imaging modalities usually provide sufficient information; however, it should be considered when ultrasonography is not available. Thoracic radiographs are indicated in cats with renal neoplasia to detect evidence of metastasis associated with primary renal tumors, or findings consistent with lymphoma such as a mediastinal mass or pleural effusion.

Microscopic Examination

Cytological evaluation of renal aspirates is the easiest method for making a diagnosis of renal lymphoma (Figure 68-8). It can be performed blindly or with ultrasound guidance and usually requires minimal or no sedation. Before renal aspiration, performing abdominal ultrasound is appropriate to distinguish between cystic renal diseases (e.g., polycystic kidneys) and

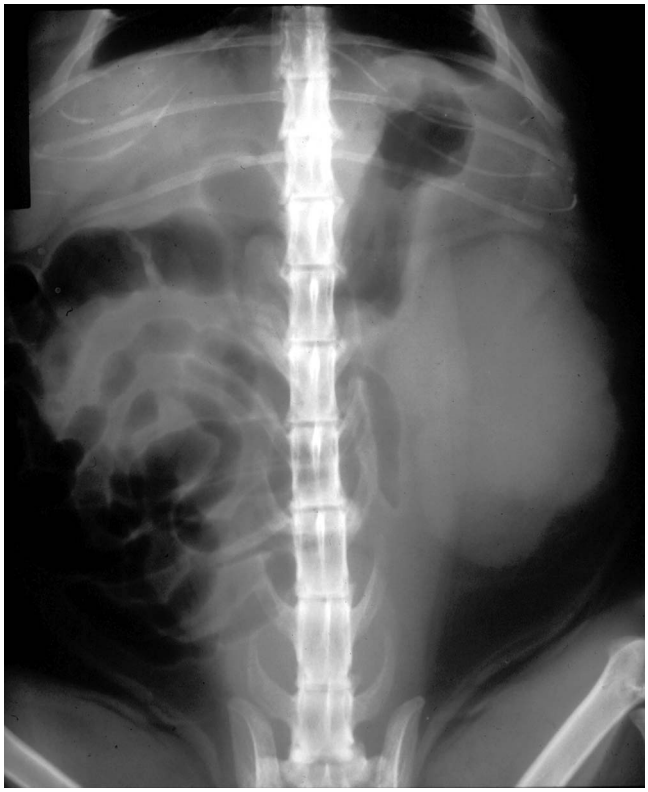

Figure 68-6. Ventrodorsal abdominal radiograph from a cat with palpably enlarged kidneys. Normally, feline kidneys are two to three times the length of the second lumbar vertebrae. Note the presence of bilateral renomegaly, which occurred secondary to lymphoma in this cat. Because of overlying intestines, the right kidney is more difficult to visualize.

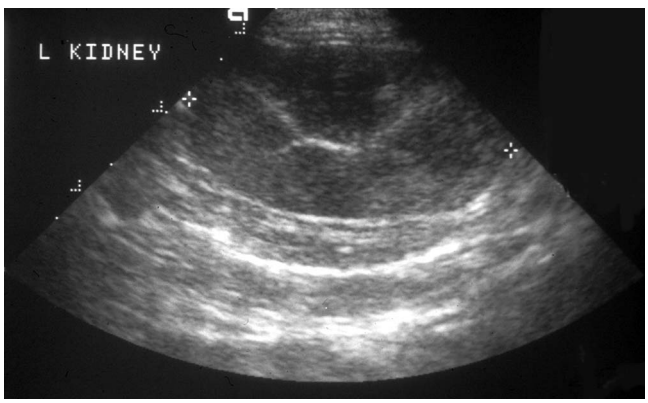

Figure 68-7. Renal ultrasound of the cat described in Figure 68-6. Note the presence of multifocal, hypoechoic areas throughout the renal parenchyma. These findings are consistent with lymphoma, which was confirmed in this case by cytological evaluation of a renal aspirate.

findings consistent with lymphoma. In addition, ultrasonography may reveal localized lesions, which are better aspirated with ultrasound guidance. Detailed information on techniques of renal aspiration are available elsewhere.[40,60,61]

If a unilateral primary renal tumor is suspected on the basis of clinical and laboratory findings and diagnostic imaging, consideration of exploratory celiotomy instead of fine-needle aspiration is appropriate. Celiotomy allows collection of samples for histological evaluation and definitive treatment (i.e., nephrectomy). Histological examination is preferred for

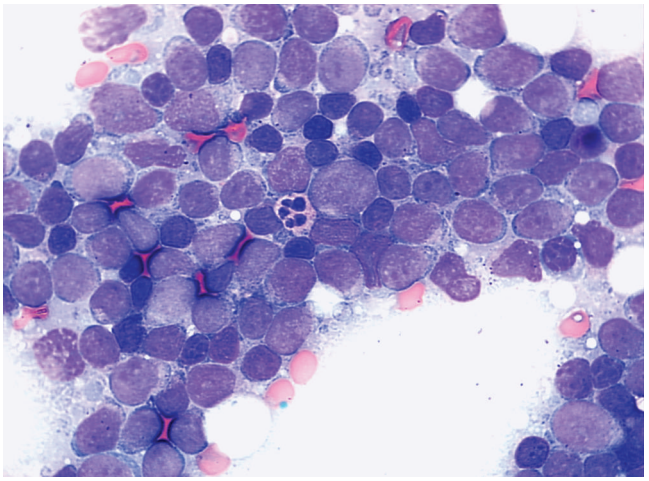

Figure 68-8. Cytological evaluation of a fine needle aspirate from the kidney of a cat with bilateral renomegaly. Note presence of occasional red blood cells (7 to 8 µm in diameter), small lymphocytes, and a neutrophil in the center; the predominant cells are lymphoblasts. These findings are consistent with lymphoma (Diff-Quik, original magnification 100×).

definitive diagnosis of primary renal neoplasia and determining tumor type. Although samples of renal tissue may be obtained percutaneously for cytological or histological examination, this carries the risk of seeding the abdominal cavity or wall with malignant cells.

Treatment

The preferred treatment for unilateral primary renal tumors is surgical excision of the affected kidney. Before surgery, diagnostic imaging studies should be performed to determine the clinical stage or extent of tumor involvement. Cats with no evidence of disease outside the kidney are the best candidates for surgery. In addition, renal function should be evaluated to determine if the contralateral kidney can sustain the patient postoperatively. The ideal method is measurement of individual kidney glomerular filtration rate with nuclear scintigraphy.[62] Most renal tumors are malignant, and systemic treatment (e.g., chemotherapy) seems reasonable as adjuvant therapy. Because renal tumors are so uncommon in cats, however, no studies are available on which to make recommendations regarding chemotherapy. In dogs, chemotherapy for renal carcinoma has been unrewarding.[63]

Chemotherapy is indicated for cats with renal lymphoma (see Chapter 66 for details). Lymphoma is a systemic disease and even cats that have unilateral renomegaly are best managed with chemotherapy, not nephrectomy.[10] Prognosis may depend on FeLV status, severity of azotemia, and initial response to treatment.[10]

Management

Concomitant disorders may require additional management in cats with renal tumors. Chronic renal failure should be managed with a renal failure diet, anemia control, and fluid, electrolyte, and acid/base balance maintenance (see Chapter 42 for additional information). Cats with FeLV and/or FIV infections may need supportive care and treatment for complications (e.g., anemia, secondary infections) associated with these viral infections.[64,65]

Prevention

Preventive measures are unknown for primary renal tumors; it may be possible to decrease occurrence of renal lymphoma in some cats, however. Keeping cats indoors and avoiding high-risk behaviors (e.g., fighting, close contact with potentially infected cats) decreases exposure to viral infections.[64,65] Vaccination of cats that live with infected cats or that go outdoors may decrease risk for FeLV infection.[65] Preventing exposure to passive tobacco smoke should be considered for all cats.

Pathological Findings

Approximately 95 per cent of feline primary renal tumors are malignant; a few benign adenomas have been reported. One cat with a renal adenoma developed a pulmonary nodule 7 months after nephrectomy; histological examination of the nodule revealed adenocarcinoma, which was suspected to be a metastatic lesion from the renal tumor.[8] In a study of cats with primary renal tumors, three of four tumors diagnosed originally as adenoma were reclassified as malignant tumors (i.e., carcinomas, transitional cell carcinoma) after histopathological review.[9] These findings suggest that differentiation between adenoma and adenocarcinoma may be difficult, even with histological evaluation.

Although all malignant renal tumors have the potential to metastasize, this has been reported most commonly in cats with renal carcinomas or transitional cell carcinomas.[6,9,20] In one study, metastatic disease was detected in nine of 14 (64 per cent) cats with clinical staging performed; the most common sites were lung, liver, abdominal cavity, and adrenal gland.[9] In another group of cats with primary renal tumors, metastasis was reported in nine of 18 (50 per cent) patients; metastatic sites included abdominal tissues (perirenal soft tissues, adrenal gland, omentum, opposite kidney, sublumbar lymph nodes, spleen), thoracic structures (lungs, tracheobronchial lymph nodes, heart, pulmonary arteries, diaphragm), and miscellaneous tissues (meninges, eye, skeletal muscle, lumbar vertebrae).[6]

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Chapter 69

Treatment-Related Emergencies in Feline Oncology

M. Raquel Brown and Kenita S. Rogers

HEMATOLOGICAL TOXICITY

Cytopenia can result from myelotoxicity associated with chemotherapeutic drugs, bone marrow invasion by the tumor (myelophthisis), or decreased survival of circulating blood cells. Chemotherapeutic agents kill primarily actively dividing cells.[1] Cells of normal tissues are damaged, but most recover with time. In contrast, bone marrow progenitor cells and lineage-specific precursor cells are especially sensitive to chemotherapy because of their short life span and inability to constantly renew themselves.[2] Bone marrow stem cells tend to be spared, because they are not rapidly proliferating cells.[3]

Myelophthisis is common with the various leukemias. Crowding out of normal bone marrow cells probably is not a complete explanation for these cytopenias, because tumor-secreted cytokines likely alter local cell kinetics and metabolism.[4] Several theories exist regarding the pathogenesis of decreased marrow production in myelophthisic states. They include competition between tumor cells and myeloid cells for nutrients, occlusion of the blood supply to the marrow by tumor cell thrombi, lysis of marrow cells by adjacent tumor cells, and production of substances by tumor cells that actively inhibit normal marrow cell development. Myelophthisis-induced bone marrow suppression often involves multiple cell lines. However, the earliest change may be neutropenia because the neutrophil has the shortest half-life of the common circulating cells (neutrophils 7.4 hours, platelets 21.5 hours, and erythrocytes 73 days).[5-7]

Decreased survival of circulating blood cells resulting from immune-mediated mechanisms has been described to occur secondary to neoplasia.[8] Naturally occurring immune-mediated neutropenia in animals has not been reviewed in great detail, so its prevalence is unknown.[8-12]

Cytopenias from chemotherapy-induced bone marrow suppression range from mild to life threatening (Table 69-1). The degree of cytopenia depends on multiple factors, including the mechanism of action of the drug (cell-cycle nonspecific agents cause more severe cytopenia), dose used, patient age (young patients have highly cellular bone marrow, so the myelosuppression is less severe), neoplastic involvement of the bone marrow (myelophthisis), prior chemotherapy use (depletes the bone marrow stem cell population), and nutritional status of the cat (malnourished animals are more susceptible to the effects of chemotherapy because they are in a negative metabolic balance). Additionally, the use of multiple agents with superimposed myelotoxicity results in a higher degree of cytopenia than when one drug is used as a solitary agent.[1]

Neutropenia

Neutropenia often is the dose-limiting effect of chemotherapy. The nadir typically occurs 4 to 7 days after treatment, and the neutrophil counts return to normal values within 36 to 72 hours.[1] Lomustine and carboplatin are two notable exceptions to this generalization. Lomustine's nadir occurs variably between 7 and 28 days after treatment, and the counts sometimes do not return to normal for up to 14 days after the nadir.[13] Carboplatin has been shown to have a neutrophil nadir that occurs on day 17.[14] Chemotherapy-induced neutropenia is not always predictable and may occur even though the patient has received the drug previously without adverse effects.[15]

Severity of neutropenia is the most important risk factor for developing an infection.[16] In human beings, and presumably cats, the risk of infection correlates inversely with the neutrophil count, and serious infections are likely to occur when the count falls below 1,000 cells/μl.[17] As the neutrophil count decreases, duration of neutropenia becomes an increasingly important factor as well.[16]

Prophylactic antimicrobial therapy should be considered for the asymptomatic, afebrile cat whose absolute neutrophil count is 500 to 1000 cells/μl. Infections often result from organisms in the normal flora of the gastrointestinal tract, nasopharynx, and skin. Therefore antimicrobial selection should target the reduction of the gram-negative and gram-positive organisms most often responsible for infections (*Escherichia coli, Klebsiella* spp., *Enterobacter* spp., *Staphylococcus* spp., and *Streptococcus* spp.).[16,18] Drug choices for prophylactic therapy are presented in Table 69-2. These patients should be treated as

Table 69-1 | **Commonly Used Chemotherapeutic Drugs and Their Potential to Cause Myelosuppression**

MILD	MODERATE	SEVERE
Corticosteroids	Chlorambucil	Doxorubicin
L-asparaginase	Vincristine ($0.7\ mg/m^2$)	Cyclophosphamide
Vincristine ($0.5\ mg/m^2$)	Methotrexate (low dose)	Cytosine arabinoside
Bleomycin	Melphalan	Vinblastine
		Hydroxyurea
		Actinomycin-D
		Carboplatin

Table 69-2 | **Drug Choices for Prophylactic Treatment of the Asymptomatic, Afebrile Neutropenic Cat**

ANTIMICROBIAL AGENT	DOSE	POSSIBLE SIDE EFFECTS
Trimethoprim sulfamethoxazole	30 mg/kg PO, SQ q24h, q12h	Anorexia Leukopenia Anemia
Trimethoprim sulfadiazine	30 mg/kg PO, SQ q24h, q12h	Anorexia Leukopenia Anemia
Enrofloxacin	2.5 mg/kg PO q12h	Anorexia Vomiting Blindness
Amoxicillin	11-22 mg/kg PO, IM, SQ, IV q12h	Anorexia Vomiting Diarrhea
Amoxicillin/clavulanate	10-20 mg/kg PO q12h	Anorexia Vomiting Diarrhea
Cephalexin	10-30 mg/kg PO q8h	Anorexia Vomiting Fever

outpatients with careful monitoring of serial hemograms, in addition to the owner's observation of attitude, appetite, and temperature. Antimicrobial therapy should continue until the granulocyte count is more than 2000 cells/µl.[16]

Fever, depression, or anorexia in neutropenic patients should alert the clinician to the likelihood of infection. These patients, in addition to patients with a degenerative left shift, should be assumed to have potentially life-threatening bacterial infections.[19] A comprehensive search for the offending organism(s) should be initiated by performing a thorough physical examination (looking for obvious sites of infection), a complete blood count, serum biochemical profile, urinalysis, and urine culture and sensitivity (Table 69-3). Cystocentesis should be avoided if the platelet count is less than 60,000 platelets/µl.[12] Because of the risk of introducing infection, urethral catheterization also should be avoided. Other diagnostic tests to consider, if the patient is stable and clinical signs warrant, are blood cultures and antimicrobial sensitivities (Table 69-4), thoracic radiographs, abdominal ultrasound, transtracheal wash or bronchoalveolar lavage, and cerebrospinal fluid and joint fluid analysis. Pending results of these diagnostic tests, aggressive treatment with intravenous antibiotics is indicated (Table 69-5). After starting antimicrobial therapy with the appropriate agents, reduction of fever is expected within 72 hours and the cat should appear more alert.[16] Oral antimicrobial therapy

Table 69-3 | **Approach to the Febrile, Neutropenic Cat**

- Thorough physical examination
- Acquire a minimum database (CBC, biochemical profile, urinalysis, urine culture/sensitivity)
- If clinically indicated, and the patient is stable:
  - Blood cultures/antimicrobial sensitivities
  - Thoracic radiographs
  - Abdominal ultrasound
  - Transtracheal wash/bronchoalveolar lavage
  - Cerebrospinal fluid analysis
  - Joint fluid analysis
- Initiate fluid support
  - Place intravenous catheter using sterile technique
  - Select fluid types (crystalloid, colloid, electrolyte composition) and rates based on patient need
- Monitor (depending on patient status)
  - Temperature
  - Urine output
  - Weight
  - Central venous pressure
  - Blood pressure
  - Respiratory rate
  - Oxygenation
  - Blood glucose
  - Electrolytes
  - Evidence of renal tubular changes if receiving aminoglycosides (casts, glucosuria, azotemia)
- Begin intravenous antimicrobial therapy, after obtaining appropriate cultures
- Consider using G-CSF (5 µg/kg SQ q24h)
- Adjust antimicrobial therapy
  - Based on culture/antimicrobial sensitivity results and patient response

Table 69-4 | **Recommendations for Blood Culture Sampling**

- Blood should be obtained by fresh venipuncture (not through an intravenous catheter).
- Avoid sites associated with skin contamination or loss of integrity (skin disease).
- Shave skin free of hair.
- Swab skin three times (with either 70 per cent isopropyl alcohol or an iodine-containing solution).
- Sterile gloves, syringes, and needles should be used for venipuncture.
- Swab the blood culture stopper with isopropyl alcohol or iodine before inoculation.
- Proceed with venipuncture and ensure it is clean and swift.
- Obtain 2 to 3 ml of blood per culture (microculture tubes). If insufficient blood is available, results may be invalid. Priority should be given to filling the aerobic culture bottle if collection allows for only a small volume of blood.
- Change the needle used for venipuncture before inoculation of culture bottles.
- Allow 30 or 60 minutes between collections, and use different sites.
- If the patient is receiving antimicrobial therapy at the time of culture, media containing antimicrobial removal devices should be used.

Table 69-5 | **Antimicrobial Choices for the Febrile, Neutropenic Cat**

- Ampicillin + aminoglycoside
- Cephalothin + aminoglycoside
- Ampicillin + enrofloxacin
- Cephalothin + enrofloxacin
- Imipenem + cilastatin

should continue for 1 to 7 days after the neutrophil count increases about 2000 cells/µl and the fever resolves.

Recombinant human granulocyte-colony stimulating factor (rhG-CSF) is available commercially, and has been used in cats for the clinical treatment of neutropenia resulting from chemotherapy-induced myelosuppression and in experimental settings after total body irradiation and bone marrow transplantation.[20] G-CSF is a cytokine produced by stromal cells, activated T cells, fibroblasts, endothelial cells, monocytes, and macrophages.[21,22] It stimulates the proliferation and differentiation of neutrophils from their progenitor cells, which induces a neutrophilia characterized by a left shift, an increased number of circulating progenitor cells, a shortened neutrophil maturation time, and improved neutrophil function.[23,24]

The use of G-CSF in cats has not been studied extensively. One study evaluated the use of rhG-CSF in two cats each at dosages of 3, 5, and 10 µg/kg SQ q12h for 21 days.[25] Significant elevations of peripheral blood neutrophils were observed, although a statistically significant dose-related response was not seen at these dosages in any parameter evaluated. The period of maximum neutrophilia occurred between days 10 and 14 of rhG-CSF treatment, with maximum neutrophil counts ranging from 20,370 cells/µl to 61,400 cells/µl (normal is less than 12,500 cells/µl). Neutrophil counts decreased on days 17 to 21 in the face of continued treatment with rhG-CSF. The researchers theorized that the use of heterologous rhG-CSF protein elicited the rhG-CSF antibodies in the cats, which led to a subsequent reduction of the rhG-CSF available to myeloid cells. Neutropenia developed in two cats after cessation of the rhG-CSF therapy, which was suspected to be due to the continued presence of circulating antibodies to rhG-CSF that were cross-reacting to endogenous cat G-CSF.

Colgan, Gasper, Thrall, et al[26] evaluated recombinant canine G-CSF (rcG-CSF) in five clinically normal cats at a dose of 10 µg/kg q24h for 10 days.[26] A rapid and persistent rise in circulating neutrophil numbers resulted. The rcG-CSF resulted in neutrophils that were mature and segmented. No left shift was evident at any point of the treatment regimen. Following cessation of the drug at day 10, neutrophil numbers remained high through day 16 and returned to within normal limits by day 21.

Another study examined four healthy adult cats that were given 5 µg/kg/day of rcG-CSF SQ (two cats received rcG-CSF for 42 days and two cats received rcG-CSF for 23 days).[27] Mean neutrophil counts in all four cats increased significantly within 24 hours. Neutrophil counts continued to rise until day 14 and remained elevated until the rcG-CSF therapy was discontinued. Neutrophil counts returned to pretreatment levels within 5 days of stopping therapy in both groups. This study concluded that rcG-CSF can be used safely and effectively in cats for at least 6 weeks without clinical evidence of hematological disorders resulting from antibody production.

A similar study followed five healthy young adult cats that received rcG-CSF (5 µg/kg/day SQ) for 42 days.[28] Mean neutrophil counts also increased significantly within 24 hours after receiving the first dose and remained high until the drug was discontinued at 42 days. Once treatment was discontinued, neutrophil counts returned to pretreatment values within 5 days. This study also concluded that no clinically significant toxicosis occurred with the administration of rcG-CSF in cats.

These studies suggest that the amino acid sequence may be more homologous between feline and canine G-CSF than between feline and human G-CSF. However, rcG-CSF is not available commercially and thus cannot be used in feline patients at this time.[29]

Development of feline G-CSF (fG-CSF) is underway. The homologous cytokine may be more potent and should not induce antibody production with long-term use.[20,30]

Guidelines for Use of G-CSF

Recommendations have been made to restrict the use of rhG-CSF to animals with febrile neutropenia (segmented neutrophil count less than 1000 cells/µl), prolonged severe neutropenia (less than 500 cells/µl for longer than 72 hours), or a history of febrile neutropenia with previous chemotherapy.[29] It also should not be administered from 24 hours before to 24 hours after chemotherapy is given because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy.[29] We use rhC-CSF at a dose of 5 µg/kg q24h until the neutrophil count exceeds 2500 cells/µl.

Changes in leukocyte number and morphology (including neutrophilia with a left shift, Döhle bodies, vacuolation, and toxic granulation) are expected after G-CSF administration.[31,32] The reason for the marrow myeloid vacuolation is unknown; however, it may be a component of activation of these cells.[25] These changes are normal sequelae to G-CSF administration and do not necessarily indicate sepsis.[29]

Granulocyte Transfusions

In the 1970s, the benefit of granulocyte transfusions in human medicine was studied and results were encouraging, provided that the dose of granulocytes given was not too low.[33] Despite the encouraging reports, granulocyte transfusions fell out of favor as a result of the difficulty in obtaining sufficient numbers of leukocytes from normal donors. Renewed interest in this therapeutic strategy has occurred with the use of G-CSF increasing the collected number of granulocytes by fivefold to sixfold.[35,38] Granulocyte transfusions have not been studied extensively in veterinary medicine because of the expense and technical difficulty involved. Large volumes of blood must be processed to recover sufficient neutrophils to treat one adult animal.[16] Granulocyte cross-matching is necessary to minimize loss of effectiveness from alloimmunization during long-term transfusion support, and irradiation of granulocyte concentrate is recommended to minimize transfusion-associated graft-versus-host disease in patients with severe immunosuppression. With these obstacles, granulocyte transfusion is not likely to be a therapeutic option for the febrile neutropenic cat in the near future.

Thrombocytopenia

Thrombocytopenia is believed to be the most common platelet disorder recognized in feline medicine, with the prevalence rate reportedly to be 1.2 per cent[36,37] (see Chapter 60). One study of 41 thrombocytopenic cats noted that 20 per cent of these patients had neoplasia.[37] The mean platelet count of these cats was 29,000/µL (reference range, 300,000 to 800,000/µL) before any chemotherapy or radiotherapy was received. Neoplasia may induce thrombocytopenia by a variety of mechanisms, including decreased platelet production, increased platelet destruction, increased platelet utilization, and platelet sequestration (Table 69-6).[38] Decreased platelet production may be

Table 69-6 | **Neoplastic Conditions Associated with Thrombocytopenia in Cats**

DECREASED PLATELET PRODUCTION
Myelophthisis
Myelodysplasia
Feline leukemia virus infection
Feline immunodeficiency virus infection
Chemotherapy
INCREASED PLATELET DESTRUCTION
Immune-mediated thrombocytopenia
Shortened platelet survival
Microangiopathy
INCREASED PLATELET UTILIZATION
Disseminated intravascular coagulation
Tumor-associated hemolysis
INCREASED PLATELET SEQUESTRATION
Splenomegaly
Vascular tumors

a result of myelophthisis causing direct crowding of the bone marrow cells by infiltrating cancer cells, or perhaps by tumor cell secretion of factors that suppress hematopoiesis. Chemotherapeutic agents, such as carboplatin and lomustine, also may suppress platelet production directly.[13,14] Immune-mediated platelet destruction may play a role in feline neoplasia-related thrombocytopenia, although antiplatelet and antimegakaryocyte antibodies have only been documented in the serum of canine and human cancer patients.[39-41] A shortened platelet life span also has been documented in human and canine cancer patients.[42,43] Disseminated intravascular coagulation (DIC) or chronic hemorrhage may result in platelet consumption. Platelet sequestration may occur with an enlarged spleen or vascular tumors, such as hemangiosarcoma or splenic mastocytosis.

Treatment of cancer-related thrombocytopenias is focused on removal or inducement of remission of the inciting tumor, if possible. If clinically significant thrombocytopenia secondary to chemotherapeutic agents is detected, the offending drug should be discontinued or the dosage lowered on subsequent cycles. Aspirin or aspirin-type drugs should be withheld from these patients because of their effects on platelet function. If the thrombocytopenia is severe, the cat should be kept in a quiet, padded environment. Fresh platelet concentrates or fresh whole blood may be needed in patients with active bleeding. For cases secondary to immune-mediated thrombocytopenia, immunosuppressive drugs such as corticosteroids may be of benefit (see Chapter 60). Recombinant human thrombopoietin is available; its use in veterinary medicine is the subject of ongoing studies.

Anemia

Anemia is one of the most common paraneoplastic syndromes (PNS) seen in veterinary and human oncology.[44] Approximately 20 to 25 per cent of human cancer patients have PNS anemia, and although the exact incidence of PNS anemia in veterinary oncology is unknown, it is thought to be a significant problem. One or more mechanisms may be involved in any cancer patient's anemia (Table 69-7).

Anemia of chronic disease (ACD) often is mild to moderate and is characterized by a normocytic, normochromic anemia.

Table 69-7 | **Causes of Anemia in Cancer Patients**

Anemia of chronic disease
Blood loss
Bone marrow invasion/myelophthisis
Bone marrow suppression by chemotherapeutic agents
Immune-mediated destruction
Pure red blood cell aplasia
Microangiopathic hemolytic destruction
Iron deficiency

This anemia is due to disordered iron storage and metabolism, shortened erythrocyte life span, and decreased bone marrow response (although bone marrow cellularity is normal).[45] This usually is not a clinically serious anemia and treatment therefore is directed primarily toward control of the associated tumor.

Blood loss anemia may occur secondary to active growth of a tumor invading vascular structures, any ulcerated tumor, and surgical procedures. Repeated blood collection for diagnostic purposes also may be a contributing cause. Because of decreased hemoglobin content, the erythrocytes in blood loss anemia become microcytic and hypochromic over time if the chronic blood loss is external. Treatment again is directed at controlling the primary tumor, and blood transfusions if necessary.

Bone marrow invasion (myelophthisis) is common with various leukemias. In addition to crowding out the normal marrow, this anemia probably is due to a remote effect of the tumor on bone marrow function, erythrocyte metabolism, or erythrocyte kinetics that is caused by tumor-secreted cytokines.[46] Controlling the tumor and supportive medical care are the primary goals of treatment.

Chemotherapy-induced anemia is common in human cancer patients, probably because of stem cell depletion that results from higher doses and repeated courses of chemotherapy.[47] In veterinary oncology patients, with quality of life the primary goal, chemotherapeutic agents tend to be given less intensively. Therefore the anemia seen in cats receiving chemotherapy is rarely of clinical significance because the hematocrit typically is greater than 20 per cent.

Immune-mediated hemolytic anemia (IMHA) may be associated with many tumors, especially feline leukemia virus–related myeloproliferative diseases.[48] Autoagglutination is documented commonly in feline IMHA but must be distinguished from rouleaux (see Chapter 59). A positive Coombs test must be interpreted with caution because a positive test may occur in anemic patients with infection of *Mycoplasma haemofelis* (see Chapter 63), feline immunodeficiency virus, feline infectious peritonitis, and numerous chronic inflammatory diseases. In tumor-related IMHA, control of the neoplastic process is the treatment of choice; however, if this is not possible and a definitive diagnosis has been made, immunosuppressive therapy (e.g., prednisolone, 4 to 8 mg/kg PO daily) may be warranted. Azathioprine or cyclophosphamide also may be beneficial.

Microangiopathic hemolytic destruction is a secondary phenomenon to hemolysis and usually is due to fibrin deposition and/or endothelial damage, such as seen with DIC and erythrocyte shearing secondary to hemangiosarcoma.[45]

Chronic hemorrhage resulting in iron deficiency anemia may occur with intestinal neoplasms, transitional cell carcino-

mas, gastrointestinal ulcers, and thrombocytopenia. Mean cell volume (MCV) generally is normal in acute iron deficiency, but as the iron-deficient state persists, the MCV may drop below reference range. As time progresses, the mean cell hemoglobin concentration (MCHC) may decrease, although this occurs rarely in cats.[49] Controlling the primary tumor and iron supplementation are the indicated treatments.

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Chapter 70

Supportive Medical Care and Pain Management in Feline Cancer Patients

M. Raquel Brown and Kenita S. Rogers

Although hematological toxicity is a common complication associated with the treatment of the feline cancer patient, successful management of these patients requires addressing many other issues. Managing a cancer patient's pain must be a primary goal, whether the client pursues definitive treatment, palliative therapy, or just wishes to provide the pet with the best quality of life possible. Gastrointestinal toxicities (anorexia, vomiting, diarrhea), extravasation injury, acute tumor lysis syndrome (ATLS), and hemorrhagic cystitis also are potential complications about which each clinician should be familiar in order to achieve successful management of cancer patients. The following is a brief review of the most current literature regarding human beings and cats on each of these topics.

CANCER PAIN MANAGEMENT

Pain is the among the most common symptoms associated with cancer and affects about two thirds of human patients.[1-3] In human beings, pain is the most feared consequence of cancer.[4-7] In the past, many obstacles existed to effective pain relief in human cancer patients: inadequate pain management training, lack of understanding of pain pathophysiology, poor physician-patient communication, low priority of pain management in overall patient care, fear of producing addiction, and failure to use existing knowledge and medicine.[6,8,9] Although similar statistics are not available for feline cancer patients, pain must be an important and frequently ignored aspect of veterinary cancer therapy, presumably for the same reasons as in human cancer patients.[10] More feline owners are electing to prolong their pets' lives despite a diagnosis of cancer. Therefore, veterinarians are faced with the difficulties of providing easily administered, convenient, reasonably priced, safe, and effective pain management to patients unique in their metabolism and reactions to various analgesics and often difficult to assess regarding their expression of pain and response to analgesics. The focus in many patients must be on alleviation of suffering and improvement of the patient's quality of life.

Cancer Pain Etiology

Cancer pain may be due to the direct effects of tumor progression (e.g., direct tumor invasion into bone, obstruction of lymphatics), cancer treatment (e.g., surgery, radiation therapy, chemotherapy), diagnostic procedures (e.g., bone marrow examination), or chronic disease (e.g., osteoarthritis).[11] The pathophysiology and mechanisms of pain are beyond the scope of this chapter; therefore the reader is directed to related resources.[10-12]

Cancer Pain Treatment

For pain caused by tumor progression or infiltration, primary therapy consisting of surgery, radiation therapy, and/or chemotherapy should be pursued if possible.[10] Staging of the patient, identification of concurrent underlying diseases, financial and time constraints of the owner, and the owner's ethical beliefs often direct treatment choice. The reader is referred to more comprehensive sources for information on perioperative pain management, sedation/anesthesia protocols, and recognition of pain in animals.[13-16] This section focuses on medications the owner and veterinarian can administer easily on an outpatient basis for relief of chronic pain in the feline cancer patient.

Ease of administration, affordability, safety, and lack of adverse side effects are important when an analgesic is chosen for at-home care of feline cancer patients. Before any medication is dispensed, a thorough history, physical examination, complete blood count, serum biochemical profile, and urinalysis should be obtained. Abnormalities in renal and liver function, other concurrent diseases, and medications that the patient is receiving must be accounted for before an analgesic drug is prescribed. Once baseline information is obtained, medication may be chosen that meets the needs of the patient, and what the owner can afford, has time to administer, and has the skills to administer. Whatever medication is selected, potential side effects and monitoring protocols should be discussed with the owner to ensure maximal quality of life for the patient and their human families.

Table 70-1 | **Analgesic Drug Therapies for the Feline Cancer Patient**

DRUG	ROUTE OF ADMINISTRATION	DOSE
Butorphanol	PO	0.2-1.0 mg/kg q4-8h
Buprenorphine	PO	5-10 µg/kg q6-8h
Fentanyl patch	Transdermal	See Table 70-2
Piroxicam	PO	0.3 mg/kg q48-72h
Aspirin	PO	10-20 mg/kg q48-72h
Carprofen	PO	1 mg/kg q24h, *1 to 2 doses only*
Ketoprofen	PO	2 mg/kg loading dose, then 1 mg/kg q24h *3-5 days maximum*
Meloxicam	PO	0.2-0.3 mg/kg loading dose, then 0.1 mg/kg q24h for 3-4 days. 0.025 mg/kg may then be administered 2-3 times per week, *not to exceed the 0.1 mg/week maximum*
Prednisone	PO	1 mg/kg q24h, then as needed

Table 70-2 | **Fentanyl Patch Dosing Guidelines**

PATIENT WEIGHT	PATCH SIZE
<3.2 kg (7 lb)	Not recommended
3.2 to 6.8 kg (7 to 15 lb)	25 µg/hr
6.8 to 18.2 kg (15 to 40 lb)	50 µg/hr

Table 70-3 | **Fentanyl Transdermal Patch Application Guidelines**

Clip the hair over the lateral thorax or dorsal cervical region.
Do not clean the site with alcohol or scrub solution.
Remove the patch from the package, being careful to handle only the edge of the patch with your bare hands.
Apply the patch to the clipped area.
Hold the patch in place for a minimum of 2 minutes.
Determine if a bandage is necessary or not. If necessary, apply a light wrap and label with the date, dose of the fentanyl patch, and initials of the person who applied the patch.
Do not use tissue adhesive to secure the patch: it may interfere with the membrane and alter the absorption to the patient.

Opioids

The most commonly used oral opiate in cats is butorphanol. This agonist-antagonist is appropriate for mild to moderate pain.[14] The oral dose ranges from 0.2 to 1.0 mg/kg PO q4-8h (Table 70-1). Side effects are uncommon, but occasional vomiting and mild respiratory depression may be seen. This is a Schedule IV controlled substance and is moderately expensive.

One of the most exciting recent discoveries is that oral administration of the veterinary formulation of buprenorphine is 100 per cent bioavailable in cats and that cats accept the medication well.[17] In a recent study of six healthy cats, location of placement of the medication (i.e., on the tongue, under the tongue, or in the cheek pouch) did not affect efficacy. No serious side effects were noted, no vomiting occurred, and food intake did not change in the 24-hour study period. Food was withheld for 6 hours before buprenorphine administration. Most cats became quiet and displayed signs of euphoria (increased purring, rubbing, and kneading with their forepaws) after receiving the drug. Buprenorphine is a partial opioid agonist effective for mild to moderate pain. It is a Schedule V controlled substance and is relatively inexpensive.

Transdermal fentanyl patches provide sustained plasma concentrations of fentanyl, a synthetic opioid compound, through a 5-day period.[18] Advantages of these patches are that they are readily available, convenient, easily applied and maintained, and well tolerated (Tables 70-2 and 70-3). Disadvantages include the 12- to 24-hour lag time until steady-state plasma concentrations are attained, the temperature-dependent release of fentanyl from the patch necessitating dosage adjustment in the febrile patient, and the limited patch size availability (not recommended for feline patients <3.2 kg). Fentanyl is a Schedule II controlled substance and the cost is reasonable if compared with the cost of veterinary administration of multiple parenteral opioids.

Nonsteroidal Antiinflammatory Drugs

By blocking cyclooxygenase and thus suppression of prostaglandin synthesis, nonsteroidal antiinflammatory drugs (NSAIDs) produce analgesia and reduce inflammation. They have not been used widely in feline patients because of their toxicities. They should be used only in healthy, young, normotensive, normovolemic cats with no evidence of gastric ulceration, bleeding diathesis, or compromised renal function.[14] Unfortunately, veterinarians often are faced with a need for analgesia in feline cancer patients that are elderly and/or have underlying renal insufficiency. In these cases particularly, the risk-versus-benefit ratio should be evaluated and potentially the dosing schedule adjusted before institution of therapy with NSAIDs (see Table 70-1). Five NSAIDs currently are used in cats: piroxicam, aspirin, carprofen, ketoprofen, and meloxicam. Gastrointestinal and renal side effects are possible with each of these products. Concurrent use of NSAIDs with corticosteroids is contraindicated because of the increased risk of gastrointestinal ulceration and perforation.

Corticosteroids

Glucocorticoids have antiinflammatory, analgesic, and antipyretic effects through inhibition of phospholipase A2, which ultimately inhibits the production of arachidonic acid. They also may benefit feline cancer patients through appetite stimulation and provision of a feeling of euphoria. Glucocorticoids are inexpensive, but chronic use can lead to increased susceptibility to infection and iatrogenic hyperadrenocorticism. Their concurrent use with NSAIDs is discouraged.

GASTROINTESTINAL TOXICITY

Although less common than myelosuppression, gastrointestinal toxicity is a relatively common complication of cancer

chemotherapy in pets. Clinical signs may include nausea, anorexia, vomiting, and diarrhea. Although all chemotherapeutic agents should be considered to have the potential to cause gastrointestinal toxicity in cats, doxorubicin and vincristine are associated most commonly with these side effects.[19-23] Cancer of the gastrointestinal system may present with the same clinical signs; therefore differentiation of clinical signs associated with the primary disease from complications of chemotherapy is important. This is especially true of gastrointestinal lymphoma in cats.

Chemotherapeutic agents cause gastrointestinal toxicity by several mechanisms: direct damage of gastrointestinal mucosa; irritation of the local gastrointestinal tract, which leads to stimulation of gut neurotransmitters and subsequent activation of the vomiting center via the vagus and sympathetic nerves; and stimulation of the chemoreceptor trigger zone (CRTZ) and medullary emetic center via stimulation of various neurotransmitter receptors.[24] Serotonin release from enterochromaffin cells in the gastrointestinal tract is important in the pathology of acute vomiting (usually occurring within 6 to 12 hours of administration of the drug).[25,26] Other neurotransmitters, such as dopamine, histamine, acetylcholine, and opiates, may be responsible for delayed vomiting (beginning 2 to 5 days after drug administration).[24,27,28]

Anorexia

Anorexia may be due to the above mechanisms or be a sequela of stress, fear, tumor-related pain, or anosmia. Efforts to reduce stress and fear should be made by offering the food in a quiet, calm environment. A variety of dry and canned foods should be offered. Canned foods should be warmed to body temperature. Owner encouragement by hand feeding also may improve the cat's food intake. Analgesics should be administered as needed to ensure the cat's comfort.

Chemical stimulation of appetite may be needed if the above attempts fail. Antiserotonin agents, benzodiazepine derivatives, prokinetics, and corticosteroids have been shown efficacious (Table 70-4). If these fail, enteral and parenteral nutrition should be instituted (see Chapter 16). Parenteral nutrition may be indicated for the patient with prolonged anorexia.[29,30]

Vomiting

Vomiting is relatively uncommon in cats receiving chemotherapy and most often is seen 3 to 10 days after the drug has been administered. Often withholding food and water for 24 hours and then gradually reintroducing them is enough to control this problem. If vomiting is prolonged or severe, prokinetics, antiemetics, and intravenous fluid therapy may be indicated. Prokinetics/antiemetics (e.g., metoclopramide), phenothiazines (e.g., prochlorperazine, chlorpromazine) and/or serotonin antagonists (e.g., ondansetron, dolasetron) often are effective (Table 70-5).

Diarrhea

Chemotherapy-induced diarrhea is uncommon in cats. In treatment for mild diarrhea, food is withheld for 24 hours and then a low-fat diet is offered during the refeeding period. Small portions of cooked chicken or turkey may be offered multiple times per day for several days. The animal's original diet then may be reintroduced slowly over a 3-day to 5-day period. If the diarrhea is more severe, other causes should be investigated.

EXTRAVASATION INJURY

Extravasation has been reported to occur in 0.1 per cent to 6.5 per cent of human patients who receive chemotherapy infusions; the reported incidence in veterinary medicine is unknown.[31-34] This often avoidable complication can lead to severe tissue necrosis and affect the treatment plans for the affected patient dramatically.

Anthracyclines (e.g., doxorubicin) and vinca alkaloids (e.g., vincristine and vinblastine) are the chemotherapeutic agents used in veterinary medicine that are most likely to cause necrosis if extravasated. Tissue damage secondary to extravasation occurs by several mechanisms.[35] Doxorubicin is absorbed locally by the cells and binds to DNA, which leads to cell death.[36] After cell death, the drug is released and causes additional death in surrounding cells. Healing is impaired and injury is chronic because of the repetitiveness of this process. In fact, several studies have found significant levels of doxorubicin in the surrounding tissues many weeks or months after extrava-

Table 70-4 | **Appetite Stimulants and Their Possible Side Effects**

DRUG CLASS	DRUG	DOSE	POSSIBLE SIDE EFFECTS
Antiserotonin agents	Cyproheptadine	2-4 mg PO q12-24h	Sedation Dry mucous membranes Paradoxical agitation
Benzodiazepines	Diazepam	0.05-0.4 mg/kg PO, IM, IV	Irritability Depression Hepatitis
	Oxazepam	2 mg/cat PO q12h	Sedation Ataxia
Prokinetics	Metoclopramide	0.2-0.5 mg/kg PO, SQ q8h 1 mg/kg/24h (CRI)	Frenzied behavior Disorientation Constipation
Corticosteroids	Methylprednisolone	0.5-1 mg/kg PO PRN	Polyuria Polydipsia Polyphagia Weight gain Diarrhea

Table 70-5 | **Antiemetics and Their Potential Side Effects**

DRUG	MECHANISM OF ACTION	DOSE	POTENTIAL SIDE EFFECTS
Metoclopramide	Dopaminergic D_2 receptor antagonist	0.2-0.5 mg/kg PO, SQ q8h	Frenzied behavior Disorientation
Serotonin	5-Hydroxytryptamine 4 receptor (5-HT_4) agonist	1-2 mg/kg/24 hours (CRI)	Constipation
Prochlorperazine	Acts centrally to block dopamine in CRTZ, emetic center, and peripheral receptors	0.1 mg/kg IM q6-12h	Hypotension
Chlorpromazine	Acts centrally to block dopamine in CRTZ, emetic center, and peripheral receptors	0.5 mg/kg IM q8h	Hypotension Tremors Diarrhea
Ondansetron	Serotonin receptor antagonist (5-HT_3 antagonist)	0.5-1.0 mg/kg PO q12-24h	Hypotension Arrhythmias Constipation
Dolasetron	Serotonin receptor antagonist (5-HT_3 antagonist)	*To prevent vomiting:* 0.6 mg/kg IV, PO q24h *To treat vomiting:* 1 mg/kg IV, PO q24h	Hypotension Arrhythmias Constipation

Table 70-6 | **Treatment Guidelines for Extravasation Injury in the Feline Cancer Patient***

CHEMOTHERAPEUTIC AGENT	CONSIDERATIONS
Vincristine Vinblastine	Immediately administer hyaluronidase (300 units) diluted with 6 ml saline (0.9 per cent NaCl) subcutaneously circumferentially in the extravasation areas Consider applying warm compresses
Doxorubicin	Administer dexrazoxane.† Apply DMSO topically and allow to dry. Repeat every 6 to 8 hours for several days. Apply ice packs every 6 to 8 hours for 24 hours. Consider immediate surgical excision of tissue if a large amount of drug extravasated.

*These antidotes are controversial. No prospective clinical trials have been performed in cats. The above are only recommendations: use with caution.
†Reported cardioprotective dose used in dogs with extravasation injury: 300-600 mg/m^2, IV, within 4 hours of extravasation and at 24 and 48 hours after extravasation.

sation has occurred in human patients.[31,37,38] Tissue damage caused by vincristine and vinblastine is due to the lipophilic solvents used in the commercial drug formulations, rather than direct DNA binding.[35]

The severity of tissue injury depends on the type and concentration of the chemotherapeutic agent and the quantity injected. Clinical signs range from immediate pain, pruritus, and erythema, to necrosis and tissue loss. Necrosis may be noted as early as 1 to 7 days after perivascular injection of vinca alkaloids but typically is identified 7 to 10 days after anthracycline extravasation. The most severe reactions are seen in patients that receive doxorubicin.

Managing the skin injury after an extravasation has occurred can be difficult and frustrating for everyone concerned. Therefore extensive efforts must be made to prevent or minimize this type of injury. If extravasation does occur, the drug infusion must be stopped immediately and as much of the extravasated fluid as possible should be aspirated back before removal of the catheter. Antidotes and treatment plans are controversial because of lack of randomized clinical trials. The following is an attempt to highlight some of the past and present approaches to handling this complication. Current recommendations for cats are summarized in Table 70-6.

Anthracycline Extravasation

Prevention of Damage

In the past, infiltration with glucocorticosteroids was recommended in veterinary medicine.[39,40] However, studies have shown that inflammation is not prominent in the etiology of tissue necrosis and that locally injected corticosteroids are ineffective as antidotes for the treatment of doxorubicin extravasation.[40-45] One study suggests that corticosteroids may be harmful even when used as a high intradermal dose.[46]

The manipulation of local pH by sodium bicarbonate injection into the extravasation site also has been postulated to decrease the cellular uptake of doxorubicin or increase its removal from the area.[47] Use of this approach also has been discouraged because of the potential of sodium bicarbonate to produce tissue necrosis when extravasated and by experimental evidence that an alkaline pH may increase cellular uptake of anthracyclines in tissues.[48-50]

Topical application of dimethyl sulfoxide (DMSO) had been recommended for the treatment of anthracycline extravasation in human patients. Several animal experiments, human case reports, and prospective human studies have described the efficacy of intradermal or topical DMSO.[51-55] Its high efficacy may be related to its potent free-radical scavenging properties.[51,55] Side effects are mild and include a local burning sensation and the characteristic odor of DMSO.[56]

Dexrazoxane, a catalytic topoisomerase II (the cellular target of anthracyclines) inhibitor, has been advocated recently in human medicine for the treatment of anthracycline extravasation.[56] Multiple animal studies and human case reports have shown promising results.[56-60] Although a single injection has been shown to reduce the size of the wound and duration of healing, triple dosage appears to be effective at completely preventing lesions.[58] The first injection is administered up to 3 to

6 hours after extravasation and the second and third injections are administered on days 2 and 3, respectively.[59,61] Side effects noted thus far in human beings include transient elevations in liver transaminases (twice the upper limit for less than 7 days) and transient leucopenia.[59] Cost and availability may limit its use in veterinary medicine.

Topical cooling with ice packs also has been recommended in human medicine, based on the observation that hyperthermia enhances the cytotoxicity of anthracyclines while cooling significantly decreases doxorubicin-induced skin toxicity.[32,62-64] The optimal duration of local cooling is unknown: cooling for as little as 45 minutes to intermittent cooling for up to 24 hours has been advocated.[63,65]

Experimental animal studies have shown a beneficial effect of vitamin C infiltration, heparin fractions, hyaluronidase, N-acetyl-cysteine, and α-tocopherol in the prevention of anthracycline-induced ulceration.[66-70] Their clinical usefulness in human and veterinary medicine remains to be determined.

Treatment of Ulcerations

If tissue injury occurs, ulceration likely will follow. Ulcers subsequent to chemotherapy extravasation do not heal readily because they lack granulation tissue and little peripheral epithelial ingrowth occurs.[61] If injury is mild, topical antimicrobials, Elizabethan collars, and daily bandage changes may be needed. Management of more severe injuries may necessitate surgical debridement and reconstruction.

Promising ulcer treatments include the use of granulocyte-macrophage–colony stimulating factor (GM-CSF) and granulocyte–colony stimulating factor (G-CSF) injections administered at the site of the doxorubicin-induced tissue necrosis. Several animal studies have shown this to be beneficial.[72,73] One human patient with two doxorubicin-induced extravasation injuries had one lesion heal with injections of GM-CSF, but no improvement was seen with the other wound that was treated with G-CSF.[74] In the experimental setting, hyperbaric oxygen therapy also has been shown to have a beneficial effect on ulcer healing when given twice daily compared with no hyperbaric treatment.[75] No studies evaluate its use in human or veterinary medicine.

Vinca Alkaloid Extravasation

Hyaluronidase, an enzyme that degrades hyaluronic acid and improves the absorption of locally injected drugs, has been shown to reduce the risk of vinca alkaloid extravasation progressing to skin necrosis.[76] It is the treatment of choice currently in human medicine.[61] In one report, four dogs received 300 units of hyaluronidase diluted in 6 mL of saline (0.9 per cent NaCl) that was administered circumferentially in the extravasation area.[71] Treatments were administered weekly until clinical signs were no longer observed. All dogs responded well to the treatment, and no adverse side effects were reported.

In contrast to anthracycline extravasation, topical warming is recommended for vinca alkaloid extravasation.[33,77] One study found topical skin heating to reduce vincristine ulceration significantly and topical skin cooling to increase vinca-induced skin ulcers significantly.[77] No published clinical trials or reports evaluate the efficacy of topical warming in cats or dogs experiencing vinca alkaloid extravasation injury in the veterinary literature at this time. Hydrocortisone, diphenhydramine, sodium bicarbonate, vitamin A cream, calcium leucovorin, and isoproterenol have been ineffective vinca alkaloid antidotes in experimental animal studies.[31]

ACUTE TUMOR LYSIS SYNDROME

ATLS is described as the biochemical disturbances that occur as a result of rapid destruction of tumor cells with subsequent synchronized massive release of cellular breakdown products sufficient to overwhelm excretory mechanisms and the body's normal capacity to reuse these products.[78] It was first described in 1973 in human patients with Burkitt's lymphoma who died within 2 to 3 days after initiation of chemotherapy.[79] Although this syndrome is well recognized and reported in the human literature, only five dogs and one cat with ATLS have been reported in the veterinary literature.[80-88]

The cardinal signs of ATLS in human patients are hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia, which are attributed to rapid cell lysis and subsequent release of large volumes of intracellular substances, which overwhelm the body's renal excretory abilities.[80] The subsequent hyperkalemia may result in clinical signs such as lethargy, muscle weakness, bradycardia, cardiac arrhythmias, and death within 12 to 24 hours after receiving chemotherapy. Hyperphosphatemia has been associated with oliguria, anuria, azotemia, or acute renal failure. Hypocalcemia may occur because of the rapid formation of calcium phosphate salts.[90,91] The patient usually is not symptomatic for hypocalcemia but has the potential to experience neuromuscular irritability and tetany.[80] Hyperuricemia results from the large quantities of intracellular purines released into the bloodstream. The purines are converted to uric acid in the liver and consequently overload the kidneys' ability to excrete the excess uric acid. Urate crystals can form and deposit in the distal renal tubules, leading to clinical signs of acute uric acid nephropathy and renal failure (nausea, vomiting, lethargy).[80] The dogs that have experienced ATLS reportedly have presented with depression, vomiting, tachycardia, pale mucous membranes, dyspnea, and prolonged capillary refill time, from 2 to 7 days after receiving radiation or chemotherapy for lymphoma. The cat presented in an agonal state with hypothermia, bradycardia, and anemia, 7 hours after being treated with radiation therapy for lymphoma.

Human patients at greatest risk for development of ATLS are those with hematological malignancies with high proliferative fractions and large tumor burdens.[80] It also can occur with solid tumors; be associated with chemotherapy, radiation therapy, or surgery; or be precipitated by a prolonged episode of fever. Acute spontaneous tumor lysis syndrome, unrelated to any of the above, also has been documented.[80,92-94] Risk factors include rapid cytoreduction of a large tumor burden, high tumor growth fraction, high serum lactate dehydrogenase activity, and pretreatment renal insufficiency.[95] All reported veterinary cases had lymphoma (three dogs and one cat with stage V lymphoma, one dog with stage IV lymphoma, and one dog with primary pulmonary lymphoma).

Aggressive fluid therapy and correction of electrolyte and acid base disorders is the mainstay of treatment. Diuresis enhances the elimination of excess phosphorus, potassium, and uric acid, and can be accomplished by intravenous fluid administration at two to three times maintenance rates. If renal function is impaired, hemodialysis may be needed until adequate

renal function resumes. Regular insulin (0.2 to 0.4 U/kg IV) followed by 2 g of glucose IV/U of insulin or sodium bicarbonate (0.5 to 1 mEq/kg IV) may be needed to correct hyperkalemia if fluid therapy alone does not work.[96] Calcium gluconate should not be administered as a treatment for hyperkalemia, because it may precipitate metastatic calcifications.[80] Phosphate binders may be implemented to help reduce hyperphosphatemia. Treatment of hyperphosphatemia often self-corrects any related hypocalcemia.[83] Sodium bicarbonate (to maximize excretion of uric acid by alkalinizing the urine) and allopurinol (to decrease the production of uric acid) are used extensively in human patients to prevent and treat hyperuricemia.[80] No clinical documentation of their use for this purpose exists in cats.

Because the optimal treatment of ATLS in cats is unknown, it would seem prudent to monitor electrolytes, acid base status, and renal and hepatic status before and after cytolytic therapy in certain patients for early detection of ATLS.[88] Cats with a large lymphoma burden or renal or hepatic insufficiency should be considered at higher risk.

HEMORRHAGIC CYSTITIS

Hemorrhagic cystitis is inflammation of the urinary bladder lining that can be a severe complication of cancer or its treatment. Oxazophosphorine-based alkylating agents, such as cyclophosphamide and ifosfamide, are the most common cytotoxic agents associated with this disorder.[97] Both chemotherapeutic agents are metabolized by the liver to form phosphoramide mustard and acrolein. Acrolein has been identified to be responsible for cyclophosphamide-induced hemorrhagic cystitis.[98] Chloroacetaldehyde, another metabolite of ifosfamide, also is toxic to the urinary endothelium and is likely responsible for the greater incidence of hemorrhagic cystitis observed with ifosfamide compared with cyclophosphamide.[99] The exact mechanisms by which these substances damage the urinary wall are unknown.[97] The urinary endothelial damage from these compounds is cumulative and generally dose-related.[100]

In human patients, pollakiuria, urgency, dysuria, and nocturia may develop in as many as 24 per cent of patients treated with oral cyclophosphamide.[101] Microscopic hematuria may occur in 7 per cent to 56 per cent of patients, and gross hematuria in 0.08 per cent to 44 per cent.[101-104] The incidence is higher with intravenous administration rather than oral administration.[105,106] Symptoms may occur immediately or years after treatment and may persist for years after the initial episode despite discontinuation of the drug.[105,107] Hemorrhagic cystitis occurred in one of 32 cats (3 per cent) in one study and three of 80 cats (3.75 per cent) in another study.[108,109]

Clinical signs include hematuria, dysuria, and pollakiuria. Urinalysis usually reveals blood with mild to moderate numbers of white blood cells and the absence of bacteria.[110] Urine cultures typically are negative, but a urinary tract infection can develop as a sequela to damaged protective mechanisms. Coagulation profiles and platelet counts are within normal limits.[100]

The most important aspect of treating hemorrhagic cystitis is discontinuation of the chemotherapy drug. Promotion of diuresis by administering prednisone and/or furosemide may speed the elimination of any remaining cyclophosphamide metabolites and decrease their contact time with the urinary mucosa.[110] Antimicrobial agents may be administered to prevent or treat secondary urinary tract infections.

Formalin and DMSO have been used in human beings and dogs if hematuria persists despite drug withdrawal.[111-114] Irrigation of the urinary bladder with 1 per cent formalin in anesthetized patients has proven effective in controlling hemorrhage by hydrolyzing proteins and coagulating superficial tissues. When 50 per cent DMSO is instilled into the urinary bladder, it blocks prostaglandin formation, enhances glucocorticoid stabilization of lysosomal membranes, and inhibits inflammation and fibroplasia.[113,114] Urinary bladder irrigation and instillation of prostaglandin F_2 has been used in human cases of refractory hemorrhagic cystitis.[115,116] Hyperbaric oxygen also has been used for its benefit of decreasing tissue edema and ensuring the necessary oxygen gradients required to stimulate continued angiogenesis, fibroblast proliferation, collagen formation, and leukocyte activation, which are required for tissue healing and repair.[115,117] No reports exist in the veterinary literature regarding use of these treatments in cats that suffer from hemorrhagic cystitis.

Prevention is the key in dealing with hemorrhagic cystitis. Administering cyclophosphamide orally instead of intravenously decreases the risk.[105] Promoting diuresis by encouragement of water intake (e.g., providing constant access to fresh water, feeding canned food with added water, offering tuna juice) and concurrent glucocorticoid administration may decrease the rate of hemorrhagic cystitis. Glucocorticoids also are thought to inhibit the microsomal enzyme systems in the liver, theoretically delaying cyclophosphamide metabolism.[108] Furosemide may decrease the likelihood of toxicosis by promoting renal perfusion and urine production. Constant access to clean litter boxes should be available.

More aggressive preventative measures are used in human medicine, including administration of 2-mercaptoethanesulphonate (Mesna), prostaglandin $F_{2\alpha}$, N-acetylcysteine, and diuretics.[100,115,116,118-121] Mesna is a sulfhydryl compound that is excreted in the urinary tract. It binds to acrolein and forms a nontoxic thioether.[118] Additionally, it inhibits the spontaneous breakdown of cyclophosphamide to acrolein in the urine.[119] Intravesical instillation of N-acetylcysteine also inactivates acrolein.[120,121] Although the incidence of hemorrhagic cystitis after cyclophosphamide administration does not warrant the routine use of these agents, mesna always is administered.

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Chapter 71

Behavior of Single Cats and Groups in the Home

Penny L. Bernstein

The estimated total population of cats living as pets in the United States is about 76 million,[1] yet little formal research exists regarding feline behavior in the home. Although a large body of anecdotal literature exists, it is based primarily on the experiences of veterinarians and applied animal behavior practitioners. Few formal scientific studies have been performed. Few studies exist of the social behavior of most wild cat species, either in natural or captive habitats, that could provide an evolutionary basis for understanding domestic cat behavior. However, studies of feral cat colonies, which provide us with a picture of domestic cat behavior unconstrained by human ownership, coupled with the few existing formal studies of cats in the home, are beginning to provide us with real insight into the social behavior of pet cats. A summary of current knowledge from formal studies of wild, feral, and domestic house cats is provided here in an effort to help veterinarians better understand the social behavior of the cats they see in practice so that they can better advise their clients.

THE SOCIAL BEHAVIOR OF WILD AND FERAL CAT GROUPS

Felid Classification: Origins of Behavior

Domestic cats currently are classified as *Felis catus*. Evidence in murals and tombs suggests they were well domesticated in Egypt by 4000 years ago,[2] and recent findings indicate they may have been important companions to human beings as long as 9500 years ago.[3] They are classified in the *Felis* or "domestic cat" phylogenetic group, which is considered fairly old among the Felidae at about 6 million years of age; only the Puma and Lynx lines are thought to be older.[4] Based on morphological and genetic evidence, domestic cats are allied closely with European *(Felis silvestris)* and African wild cats *(Felis lybica),* and all three often are considered subspecies *(F. s. catus, F. s. sylvestris, F. s. lybica).*[4,5] Currently, domestic cats are considered most closely related to the African wild cat, and genetic studies suggest *lybica* diverged from the European wild cat approximately 20,000 years ago.[4,6]

Wild Cat Behavior and Signaling: Evolutionary Precedents

Little formal research exists regarding the behavior of the African wild cat, at least in part because it is primarily nocturnal and ranges over many habitat types, in many countries. Although some individuals are held in zoos (e.g., National Zoological Gardens, Pretoria, South Africa), little formal research has been performed even on these captive populations. General behavior information does exist, however, and can be found in a variety of sources, most importantly Smithers' 1983 compendium,[7] the Sunquists' 2002 volume,[8] and various websites.[6,9] Summaries are based mostly on captive studies or reports of free-ranging, adopted wild cats.

The wild cat does not seem to be particularly social in feeding situations. It rarely is seen in groups even around rich, clumped food sources, such as garbage dumps, where domestic cats often form large groups.[10] However, some evidence shows that mothers provide one another's young with food, at least in captivity; sharing of caretaking may occur in feral domestic cats, as well.[8,9,15] Home ranges have been measured in at least two studies: one reported a home range of 1 km^2 for one individual in open oak forest on hilly, rocky ground (Israel), and the other reported a home range of more than 1.6 to 4 km^2 for one male cat in Kenya.[8,9] Such variation in home range also is seen in feral domestic cats.[11] The main threat to African wild cats seems to be from hybridization with domestic cats. However, at least one recent genetic study in southern Africa found existing clear genetic separation between wild and domestic cats and advises strong conservation measures to prevent hybridization from increasing.[12]

Bradshaw and Cameron-Beaumont[13] and Sunquist and Sunquist[8] provide excellent summaries of signaling capabilities in undomesticated felids. Although much of the summarized data were based on studies of captive wild animals, behaviors seen commonly in the domestic cat had interesting similarities. This suggests that domesticated individuals already are primed to engage in these behaviors, whether their wild ancestors do so commonly in their natural settings.

In many undomesticated wild felids, urine is emitted through spraying (i.e., primarily by males) or squatting, which often involves foot scraping. Both behaviors also are found in domestic cats. Tree-scratching is widespread among undomesticated and domesticated cats and may function in a number of ways (remove loose claw sheaths, deposit scent, provide a visual signal). Object-rubbing also is typical and observations have suggested at least three distinct functions for this behavior in wild and domesticated cats, including depositing scent (saliva), picking up scent (from previously urine-marked objects), and providing a visual signal of estrus.[8,13]

Acoustic communication varies in pattern across felid groups. Some sounds, such as hisses and spitting, are common in most groups, whereas others, such as purrs and meows, seem restricted, although the difficulty in hearing these quieter calls may affect the ability to study them. Both European and African wild cats in captivity are known to purr, chatter, hiss, spit, gurgle, meow, and give male and female sexual calls (such as yowls), although the data seem more reliable for European cats.[8] Roars seem to be restricted to lions.

Visual signals involve rolling behavior primarily, usually in sexual contexts. However, rolling in wild cats has not been seen in the submissive contexts in which it is thought to occur in domestic cats.[14] Only lions so far have been described with a tail-up signal similar in form to that used so commonly by domestic cats, and the circumstances of use have not been well studied.[13] Body and face signals have not been described for species other than the lion.[13] Tactile signals are seen in many species and may include social rubbing, lying in contact, or allogrooming, although some of these behaviors have been documented only in captivity.[13,14]

Classic Studies of Feral Cat Behavior

A number of researchers have examined the behavior of feral domestic cats, defined here as domestic cats with little if any deliberate or direct contact with human beings throughout a majority of their lives (in this chapter, this includes strays that were once owned but are now on their own). The study of these cats is helpful because they provide a glimpse into what domestic cat behavior can become when the constraints of living in a human-organized home (e.g., limited space, high densities, forced relationships) are removed and new problems are encountered (e.g., need to hunt for food, find shelter, avoid predators). Because these cats must deal with natural problems of food, shelter, and both interspecific and intraspecific interactions, their behavior often is considered more instinctive or "natural" than those of human-constrained "pets." They are studied to provide insight into the behavior of domestic cats in the home.

Two excellent reviews on the behavior of feral cats provide a summary of the literature.[10,11] Most recently, Crowell-Davis, et al[15] have combined these works with their own studies of farm cats to provide an excellent overview of behavior in feral groups. They also include a discussion of the implications of these studies for understanding behavior in multiple cat homes.

Macdonald, et al[10] explored free-ranging cat groups, mainly farm cats, and focused on the formation of groups by adult female cats, the dynamics of cat groups, and the relationship between behavior and epidemiology. Their research over a number of years involved more than 3000 hours of observation, including 63,000 interactions and 39,000 measurements of proximity among individuals in three feral farm cat colonies: one small, one medium, and one large.

Several important points were made in their review.[10] First and perhaps most important, they stressed the relationship between group size and prey size. Group formation in felids in general, including domestic cats, seems dependent in large part on the size of prey that can be captured and the need to fend off scavengers.[10] So, for example, lions working together can take much larger prey than individuals alone and can better resist attempts by hyenas to take over a kill. However, many felids, particularly the smaller ones, do not need to take large prey to gain their necessary food intake and can hunt and eat alone. As would be expected then, feral domestic cats living on wild prey such as rabbits and rodents tend to be solitary, but those with access to clumped food sources related to human activities, such as around barns, landfills, and fishing dumps, live in groups.[10] Clearly domestic cats have a built-in flexibility in grouping behavior and are not restricted evolutionarily to being solitary. However, a trade-off seems to occur: condensing around a rich food resource may lead to an increase in disease susceptibility and the spread of pathogens. Group living may have important limits.

Second, Macdonald et al[10] noted that the feral domestic cat groups that form where food is readily available are not random aggregations; rather, cats favor the company of certain cats and avoid others.[10] Clearly they can recognize one another and form long-term relationships. These seem to be based on age, sex, social status, and bloodlines.[10] Female lineages were found to be the "building blocks" of the feral cat societies that were studied. Lineage groups were formed by adult females and successive generations of their offspring; large colonies had several lineages; smaller colonies had only one or two. Relationships within the lineage generally were "amicable" and groups tended to be hostile to outsiders. Bigger lineage groups tended to occupy the area near the central food resource around which the colony was formed, whereas smaller ones tended to be more peripheral; that is, larger groups of related individuals seemed able to dominate the food source to some extent and their offspring tended to have higher survival rates.

Adult males were not tied to a particular lineage. Some males tended to stay near the central food resource, whereas others tended to roam widely, possibly visiting other groups. This behavior did not seem dependent on bloodlines; some male offspring of lineages stayed near the female group, whereas others did not. Overall, Macdonald, et al[10] found that males roamed more often or over further distances, and females tended to stay near the central food source.

Dynamics among individuals depended on colony size and other factors.[10] Sex, age, and relatedness all seemed to play important roles, but individual identities and other aspects also seemed important. The small study colony consisted of two females of different lineages, their offspring, and one male. In this group, the females tended to stay more than 10 m away from each other but were often within 10 m of the male. They were never seen to be aggressive toward the male but often were targets of his aggression. The females often licked or rubbed the male, despite his aggressive tendencies. In the two larger colonies, males tended to be aggressive toward either adult or juvenile males, depending on which were more prevalent in the population and how many females were the subject of competition. Males did not often interact with kittens in these groups.

Age groups tended to form bonds: kittens tended to interact with kittens and juveniles with juveniles. Relatedness was important: mothers tended to spend time closer to their own offspring than to the offspring of their sisters. Death of an individual may result in unexpected changes; for example, one daughter of a female that died during the study became very aggressive toward two of her sisters but not to a third sister and not to her own two daughters. Clearly, individual adult relationships were complex and based on more than relatedness.

The constraining role of pathogens on group size and dynamics became apparent when Macdonald's group examined epidemiology in a separate, large population (50 to 80 individuals) of feral cats.[10] Pathogens were highly prevalent; 100 per cent of the population showed antibodies to feline calicivirus (FCV), feline rotavirus (FRoV), and feline herpesvirus (FHV). More than half of the group (53 per cent) were seropositive for feline immunodeficiency virus (FIV) antibodies, 96 per cent had antibodies for parvovirus (FPV), about 90 per cent had coronavirus antibodies (FCoV), and 40 to 90 per cent were infected with parasites (*Toxoplasma gondii* more than 45 per cent, *Toxascaris leonina* more than 80 per cent, *Toxocara cati* more than 90 per cent). Use of communal latrines (18 for the 50 to 80 individuals), rat prey populations that could serve as a reservoir for *T. gondii*, and communal suckling and cleaning of kittens were considered possible causes of this high pathogenicity. Clearly group living may have great costs. The benefits of being a central female (close to resources, near daughters and sisters) seem to be offset by the cost of being part of a large group, where infection can enter and spread easily. However, central individuals tended to have fewer mouth infections and wounds, perhaps because they were less likely to engage in fights and may still survive better than those on the periphery.

Liberg, et al[11] examined the role of population density on spatial organization and reproductive tactics in feral cats in a review of more than 30 studies from a number of different sites over a 20-year period (1977-1997). Again, spatial availability of food and its abundance played an important role in behavior. Although domestic cats often are said to be "flexible" in their social system, from solitary to highly social, it is still astounding to see the range of densities in which feral cats have been found, from as few as one cat per square kilometer to more than 2000 cats per km^2.[11] Individual home ranges were similarly variable: female ranges varied from 0.1 to 200 hectares and male ranges up to 1000 hectares.

Group densities and female home ranges seemed to depend primarily on food abundance and distribution. Where food was plentiful and clumped (such as landfills), densities were high and female ranges small; where food was dispersed, as when hunting natural prey, densities were low and female ranges large. Male home ranges seemed more dependent on the availability of females, especially during mating season. Overall, females in the feral colonies with rich food sources tended to stay in natal groups with little roaming, and those dependent on hunting roamed over much larger areas and were more solitary. Males tended to roam and have overlapping home ranges more often than females.

Recent Studies of Feral Cat Behavior and Implications for Cat Behavior in the Home

Crowell-Davis, et al[15] attempted to gain insight into housecat behavior through a reexamination of the literature on feral cat behavior and inclusion of their own studies of farm cats. They used these studies to attempt to understand how to introduce new members to existing groups and the development and treatment of behavior problems, such as "cat bullies" and inappropriate urination and defecation.[15]

Feral cat colonies, according to Crowell-Davis, et al,[15] basically are formed when food is abundant and/or clumped, with affiliative, cooperative relationships among related females forming the core of the group. Cats in these groups can recognize colony members versus noncolony members, and nongroup individuals are not allowed to casually approach and enter a group.[15] Individuals spend time in proximity to specific others, their preferred associates, in a variety of contexts and locations, and associates can be from the same or opposite sex. When individuals in groups are intact and sexually active, males overall spend less time near one another than in groups in which all individuals are neutered, which implies sexual competition, at least between some males. However, gender does not seem to play a role in which cats spend time near each other in feral groups in which all individuals are neutered, which makes it even more clear that individual relationships play an important role in bonding, independent of sex.[15]

Males may be aggressive to one another during female estrus, but that is not always the case, and males also may be preferred associates to one another. Both females and males are polygamous, each seeking out and mating with several individuals of the opposite sex, and individual recognition and familiarity seem to enhance the likelihood of some pairings over those between strangers. Females often aid each other in raising young by grooming, nursing, and guarding each other's kittens and may even engage in "midwifing," when one female aids another during birth. Adults of both sexes seem to play a critical role in defending kittens and helping kittens and juveniles learn appropriate hunting and social behaviors.[15]

Dominance often is considered a confusing topic in cat behavior. Building on definitions from the primate and general behavior literature,[16,17] Crowell-Davis, et al[15] describe a subordinate as an "individual who consistently submits or gives way to another as a consequence of prior experience with that individual, and the animal submitted to is considered to be the dominant in that dyadic relationship." They point out that although some species have truly linear hierarchies of dominance relationships, most animals, including mammals, do not, which makes it difficult to tell in a group who is dominant to whom.[15] Also, although dominant animals can secure resources first or drive subordinates away from resources, they do not always do so. Often subordinates notice a dominant animal and leave a situation before confrontation can occur, which makes it even more difficult for observers to tell what the animals' relationships are.

Cats, then, like most mammals, do not demonstrate explicit linear hierarchies, even in feral groups. They apparently use subtle signals to communicate their intent to take or defend a resource or leave one. These involve a dominant and subordinate staring at each other (dominant) or looking away (subordinate); stiffening the ears and rotating them to the side (dominant) or lowering them slightly or flattening them (subordinate); elevating the base of the tail while drooping the tip (dominant) or curling the tail against the thigh (subordinate); stiffening the limbs (dominant) or lowering the body or crouching (subordinate); and standing upright (dominant) or rolling over (subordinate).[15] These subtleties, coupled with the fact that

dominants do not always exert their control and subordinates often curtail the need for an encounter by avoiding it, make it difficult for observers to recognize dominance relationships in cats readily.

Cats also use sounds for communication in feral groups. These are divided into three useful working categories by Crowell-Davis, et al[15]: those made with mouth closed (purrs, trills), which are seen mostly in greeting situations; those made with mouth open but gradually closing (the typical "meow"), again used mostly in greetings or amicable interactions; and those made with the mouth held open (growls, yowls, snarls, hisses, spits, shrieks), which are used mostly in aggressive situations. Feral cats also have been seen to engage in a variety of other social and signaling behaviors, including nose-touch greetings, allogrooming, allorubbing (usually using head, flank, and tail), play, tail-up as a possible signal of "friendly" intent, and lying in physical contact during rest.[15]

Olfactory communication in feral groups involves glands, urine, and feces. Glands of the head (temporal, submental, and circumoral) are rubbed against objects and other cats. Observation of placement and timing of this behavior has led to the theory that molecules are deposited that identify aspects of the colony and label specific individuals.[15] Although glands are known to exist in the perianal area and between the digits, little is known about their possible social functions. Observing feral cat colonies, it is unclear why cats deposit urine or feces in specific ways (e.g., burying feces in the core area of their home ranges but leaving them exposed on the periphery).[15] Although marking territory has been offered as a possible explanation of urine and feces deposition, Crowell-Davis, et al[15] point out that no evidence exists that cats actually defend territory (i.e., protect a piece of land). However, urine often is used by other mammals, including the larger wild cats, to convey information about estrus, provide location information about individuals and about behavior or "emotion" (e.g., aggression or arousal), and may play these roles in feral cat groups as well.[15]

This examination of feral cat populations includes some obvious correlations to housecat behavior and valuable lessons to be learned. These lessons may be grouped into socialization issues, ability to introduce new animals to a group, grooming issues (petting), and the importance of dominance relationships.[15] In terms of socialization, feral cats have demonstrated the importance of kittens learning from their mothers and others in the group about how to interact with others and with whom to interact; that is, they are "born with the capacity to learn species-specific social skills, but they are not born with the specific skills."[15] This means that cats that were found or adopted by human beings as young kittens may have missed learning important skills from their mothers. Although this may not be a problem if such a cat is kept as a single pet in the home, or if kittens found together are kept together, it may lead to major difficulties if an owner attempts to introduce a new cat. The less socialized individuals may have difficulty recognizing and using signals of greeting, dominance, or submission and may become extremely aggressive or fearful.[15]

Feral cat colonies also demonstrate cohesiveness, recognition of members versus strangers, and patterns of interaction based on gender, relatedness, and age-related socialization (e.g., female-female relationships, mother-kitten relationships, and groups of kittens growing up together). A group of cats in a home mimic this pattern in many ways; for example, individuals that came into the house together as kittens, whether related or not, often maintain close relationships, sharing space, and allogrooming one another.[19]

Subsequently, introducing one or more new cats into a stable group can be a major problem. Based on the feral cat research, Crowell-Davis, et al[15] recommend that pet owners who want more than one cat adopt small groups of related or young individuals, such as a mother and two kittens or a small group of related or unrelated kittens, at broad intervals. They also suggest the following: (1) building up some degree of familiarity between the group and any new, strange cat before it can be introduced, as occurs in feral groups, (2) keeping the stranger behind screen doors so odors can be exchanged, and (3) exchanging bedding and materials from resting spots.

Although many others have made these observations based on anecdote and experience, Crowell-Davis, et al[15] use the information gained from the feral cat studies to provide a more scientific underpinning for these suggestions. They believe it is difficult but not impossible for strangers to enter a colony, given enough time, and sight, scent, and sound are the sensory modalities used most readily by cats to facilitate this at a distance (e.g., when a stranger cat cannot get closer without inducing aggression). Surprisingly, they do not provide any recommendations about adoption of related females, a suggestion that may be expected given the importance of female relationships in feral groups.

Rubbing on human beings and human petting of cats resembles typical cat-cat social behavior in feral colonies. Problems can arise if human beings interpret rubbing as seeking further interaction when the cat may be using it only as a passing greeting, or if people pet in areas that usually are not allogroomed by other cats, such as along the back, on the tail or at its base, or on the belly.[15] Although some cats welcome this additional allogrooming, others do not.

Dominance is subtle but important in feral cat colonies and helps cats maneuver in the group. They know whom to approach, whom to avoid, and at what times and places those behaviors will be important. In the home, having a high-ranking cat that does not make an issue over resources unless particularly interested in one at a certain time may result in a peaceful group with little overt aggression.[15] Because signals are subtle and fighting rare in these populations, owners often have a perception one cat is dominant and often can identify it but cannot explain their rationale.[19] However, having a high-ranking cat that often displays classic dominance behavior (i.e., threatening, supplanting, taking resources away from others) may lead to serious intercat aggression, extremely submissive "pariah" cats, and feeding and elimination problems when a dominant cat blocks access to important resources.[15] In these cases, owners can be advised that this is overt dominance behavior, and they may be able to help the situation by working with the contested resources. For example, they may allow the dominant cat to eat first or provide many litterboxes in different locations so that the dominant cat cannot monopolize all of them.[15]

SOCIAL BEHAVIOR IN THE HOME

Pet cats living in the home are similar to and yet distinct from their wild undomesticated cousins and feral domestic cat populations. Their living conditions provide them with shelter, food, and relief from most predators and disease, but constrain them in terms of the size and density of their living area, kinds

of food available and access to it, access to the outdoors and to appropriate areas indoors in which to eliminate waste (litterbox), and the number and kinds of companions. An additional factor is the removal of reproductive capability that is typical now for most pet cats in the United States.

Lessons About Social Behavior from Direct Observation of Pet Cats in the Home: Intraspecific Interactions

Although the information gained from studies of undomesticated wild cats and feral domestic cats can provide important context for understanding the behavior of pet cats, it cannot substitute for the insights gained from direct observation of cats in the home. It is clear from in-home observation studies that cats can and do adjust their behavior to deal with the constraints of being a pet. General patterns emerge and are frequently but not universally similar to what may be predicted from studies of feral cats. Individual behaviors and relationships clearly also play an important role, as they do in feral groups.

For example, Bernstein and Strack[19] examined 14 cats living as pets in a relatively small home (approximately 124.5 km^2 or 1340 ft^2). The seven males and seven females were unrelated and neutered and ranged in age from 6 months to 13 years at the start of the 3-month study (approximately 336 hours of observation). The first finding was that these cats could live relatively peaceably at a density of 0.1 cat/m^2 or 113,000/km^2, about 50 times greater than the highest densities described for feral groups outdoors (e.g., 2000 cats/km^2).[20] This suggests that cats are capable of dealing with social "closeness" in the home and do not have to be solitary, although, clearly, single cats can thrive. The 14 cats in the study group seemed to do this through space management, home ranges and favored spots, and tail signaling at a distance. These tactics provided information that could enable recipients to tailor their responses before contact was imminent, and so, for example, avoid aggression. Based on findings for feral cats, availability of resources likely also would be an important factor in behavior determination. This owner provided a food dish for each individual, spread water bowls and litterboxes throughout the house, and provided isolated food, water, and litter for individuals that did not venture far from a specific room because of illness or apparent avoidance behavior. This may have prevented dominant individuals from blocking access to important resources, although that was not tested in this study and was not obvious from simple behavior observation.

Home range was defined as the number of specific rooms used regularly by the cats.[19] Although the entire house was open to all individuals, they did not use all areas. Individuals had overlapping but individually distinct home ranges and males tended to have slightly larger home ranges than females (i.e., used slightly more rooms on a regular basis than females did), similar to feral cat groups. However, home ranges did not seem organized around particular groups of females in any obvious way, as it would be in feral groups with intact females. Ranges seemed determined instead by a combination of individual preference for particular rooms and approach/avoidance behavior between particular individuals. Little overt aggression occurred during the study, so actual fighting did not seem to be important in determining day-to-day movement. However, the oldest male, which also showed classic dominance behaviors of fighting, chasing and supplanting, had the largest adult home range. The kittens, two 6-months-olds and one 1-year-old, had the largest home ranges of all individuals at the start of the study. They used all 10 of the available spaces on a regular basis, which suggests they were interested in these areas and not prevented by others from entering them. Bernstein[21] demonstrated that home ranges are not determined strictly by interactions with other cats but are at least partly dependent on individual preference. In 68 single-cat households, only about 18 per cent of cats used all rooms available.

Changes occurred in home ranges during the study.[19] The most dramatic involved an adult female that increased her range from one room to four and the three kittens that decreased their ranges by dropping four to seven rooms. These occurred after the male cat that had showed classic dominance behavior died and as the kittens became 1 year old. This suggests that as the kittens developed into juveniles, they began to have preferences for rooms or for individuals and/or were beginning to be limited in some way by the adult cats. It also suggests that the individual relationships between the adult male, the adult female, and the kittens played a role in these changes.

Favored spots, specific areas in a room where cats can be found on a regular, predictable basis, are well known to cat owners but rarely have been studied formally, especially for their social rather than physical aspects (temperature, surface texture). In this group, individuals had either their own unique spots or shared spots with others, either physically or over time (e.g., time sharing, in which one individual used a spot and at a later time another would use the same spot) (Figures 71-1 and 71-2).[19] In this group, physical sharing of spots was rare. However, gender, individual relationships, and developmental relationships seemed important determinants of time sharing of spots: females tended to share spots over time with specific other females, and males with specific other males. Three spots were shared by older females with a male kitten or with an adult male that had started physically sharing with the female when he was a kitten (5 years before). This pattern suggests the cats could determine who was sharing a spot. Despite the lack of genetic relatedness, it mimics findings for feral cats, which also tend to group with specific individuals (preferred associates), usually relatives (sisters and young).

Dominance in this group was clear only in terms of a "top" and "bottom" position: one individual male displayed classic dominance behaviors and one displayed classic subordinate behaviors (i.e., always withdrew as others approached and never controlled resources). No obvious hierarchy existed beyond that and little overt aggression occurred. After the male that displayed classic dominance behaviors died, no obvious dominant cat emerged. However, the owner felt that the next oldest adult male became dominant. The only evidence in this study was elusive: this individual seemed able to go wherever he wanted and eat whenever he wanted and had the largest remaining adult home range (used the greatest number of rooms on a regular basis). He also was the first to enter an empty cardboard box that was presented as a "treat" to the cats during the study. All others waited until this male left the box before they entered.

The tail-up position was seen most frequently and coincided with individuals gathering information, monitoring the approaches of others, or approaching others and beginning nonaggressive interactions.[19] This seems similar to information reported for feral cats.[15] This tail position is seen easily and could "tag" an individual as one monitoring others and likely to engage

A

B

Figure 71-1. A and **B,** Tiger and Smokey have unique "favored spots" in the home where they regularly spend part of the day sleeping and grooming.

A

B

Figure 71-2. A and **B,** Tiger and Smokey have several "favored spots" that they also alternate. Here they are each shown using the same chair at different times of day.

in nonaggressive interactions. This allows others to decide at a distance whether to approach for further interaction. Detailed video analysis would be necessary to test this impression.

Barry and Crowell-Davis[23] examined the behavior of two-cat dyads in 60 homes, 20 of each gender combination, 10 hours each pair. All cats were neutered and considered indoor-only. They found less aggression and more affiliative behaviors and time spent in proximity than they had expected, with only 68 cases of aggression over the 600 hours of observation. Aggression seemed more related to individual relationships than to gender, age, or population density (size of home). Cats spent an average of 35 per cent of their time in close proximity (within 5 m) and male-male pairs spent the most time in close proximity, 0 to 1 m. This seems to contradict findings for feral cats, in which females are most likely to form groups. What is most valuable to note is that despite the limited spatial range and the forced proximity as indoor-only cats, all pairs were capable socially, able to manage their behavior in time and space with a minimum of aggression.

Clearly more studies are needed to allow broader patterns to emerge and provide a formal basis for understanding the behavior of single cats and groups in the home.

Lessons About Social Behavior from Examination of Human-Cat Interactions in the Home: Interspecific Interactions

Although intercat relationships are of primary importance in feral cat groups, relationships with human beings are critical for cats in the home. Obviously, human-cat interactions are important to cat survival, but they also are a social challenge for the cats and provide them with a new set of interactions they must learn to accommodate and affect cat-cat interactions. Issues of socialization, differences among breeds, general interactions (e.g., feeding, petting, sharing physical contact, letting cats outside or not), and communication are important in understanding cat behavior in the home and have been addressed by a number of researchers.

Socialization

Socialization to human beings clearly is important for cats that live in a home. If they do not interact well with people, the resulting problems could affect how and when they are fed, cared for, and interacted with, and ultimately whether they will be able to continue living in the home. Most studies have focused on kittens and indicate that a key period occurs between 3 and 7 weeks and that socialization of kittens to people becomes less effective if delayed much beyond 7 weeks.[24] As may be predicted from feral cat studies, kittens seem to socialize to human beings better if their mother is present.[24,25] Less obvious are studies that find that paternity may play a role in socialization; that is, that kittens with fathers that were friendly to human beings are more likely to be friendly than kittens whose fathers were less friendly to human beings.[25-27] The suggestion is that kittens inherit traits that make them more or less friendly or perhaps more or less bold and therefore more or less willing to approach this large, novel object for interaction. The importance of individual responses to novel stimuli, independent of their dominance ranking, was supported by findings that individual cats that were high ranking in terms of social dominance (unrestricted movement) or object dominance (food or other objects) were not always the least fearful or most likely to approach novel stimuli, whether the cats were indoor restricted or free-ranging outdoor cats.[22] This study supported the contention again that individual differences play important roles in behavior and that domestic cat group structure depends on the individual characteristics of the members, a point supported by feral cat studies and the studies of cat behavior in the home discussed in the previous section.[15,19,21,23]

Handling of kittens by human beings plays a role in socialization, especially when contact includes talking.[25-28] However, handling studies also reveal that some kittens seem resistant to change in their original types, and some friendly kittens remain friendly, whether handled or not, and some fearful kittens remain so despite handling. Certainly this finding is supported anecdotally by the many instances of people taking in feral kittens and raising them successfully as pets.

An overall scheme developed by Mendl and Harcourt[29] illustrates how complex interactions among a number of critical parameters seem to be important in the expression of "friendliness to human beings." Parameters included early social experience with mother and siblings, paternity, breed, coat color and other genetic aspects, maternal care, duration and quality of interaction with human beings (and probably timing and context), and environmental complexity. Based on this and other studies, Siegford, Walshaw, Brunner, et al[30] have developed a relatively quick, simple, and reliable test of cat temperament for adult cats and kittens in an effort to help veterinarians, shelter staff, and others assess "cat sociability, aggressiveness, and adaptability" more effectively for better treatment or adoption placement. However, few studies have assessed how or why human-cat socialization may change over time, especially for adults. That is, even though anecdotal evidence for certain kinds of change in social behavior is abundant, we know little about why seemingly well-socialized friendly cats may become less friendly to human beings over time or are unfriendly to particular individuals, or why unfriendly, poorly socialized cats become more friendly over time.

Breed Effects

Only a few studies have examined the influence of breed on human-cat interactions. Mendl and Harcout included it in their scheme of factors that affect socialization.[29] However, most studies deal with subjective ratings of character differences among breeds and seek to link behavior differences with human needs and expectations for a pet.[31,32] However, Turner conducted a study that combined people's subjective assessment of breed traits with direct observations of those same people interacting with their own cats of those breeds.[33] He found that differences in ratings were supported by differences in actual interactions. People rated Siamese and Persian breeds as more socially interesting, better behaved, and more interactive than nonpedigreed cats. These assessments were borne out by direct observation of how the responders interacted with their own pets. This suggests that selective breeding has resulted in breeds that are more predictable in their behavior and therefore better able to be assessed by owners for their value as pets. However, little work has been done beyond this, and feral cat studies do not provide any additional information; pedigreed cats rarely are mentioned.

Human Effects

Some experimental studies have examined the influence of the person on human-cat interactions. Women tend to be more involved in the care of cats than men[25,34] and tend to approach cats differently, which results in different responses by the cats.[35] For example, when cats were introduced into a room in which a stranger man, woman, boy or girl was seated, human interaction made no difference in the cats' reaction. The cats were likely to approach or not at equal rates. However, they reacted differentially to people depending on how people approached them. Men tended to stay seated, whereas women usually went down to the level of the cat, which resulted in more positive interactions. Children tended to approach rather than wait for the cat to approach them, but boys usually followed the cat if it attempted to retreat, which resulted in less positive interaction.[35] One study examined attitudes of elderly versus young cat owners and found that elderly cat owners seemed more accepting of the "independence" of their cats than younger adults. These findings may be useful to veterinarians and shelters in several ways. For example, discussion about care may best be held with the adult female of a household, evaluation of behavior problems may include questions about the behavior of children or adolescents in a home, or men may be advised to approach and interact more with cats if problems occur. Shelters may use such information to make more appropriate matches between cats and people (e.g., perhaps matching an aloof cat with an elderly man living alone who is more likely to accept its independent nature).[30]

Direct Observation of Human-Cat Interactions in the Home

Although the most obvious way to answer questions about human-cat social behavior in the home would be to observe human-cat interactions there, surprisingly few studies have done so. Mertens[34] demonstrated the complexity of human-cat interactions as they occur naturally in the home. In this study, she observed 72 cats interacting with 162 people over a 12-

month period, in sessions lasting 210 minutes each. She attempted to reduce observer effect by acting like a normal visitor to the house, such as talking with owners and sitting and standing in rooms as a visitor might, although she did not interact with the cats. She was able to examine the social events engaged in by the people and their cats, including proximity, approach/withdrawal, and initiation and duration of interaction.

Generally, interaction levels were low and most interactions were of fairly short duration (1 minute or less). Single cats tended to stay closer to owners for longer periods of time and have more interactions with owners than did multiple cats. Human beings tended to make close approaches (within 1 m) to the cat more often than the reverse, but when the cat did initiate a close approach, person and cat stayed within 1 m for longer periods of time. Adults and children interacted differently with the cats. For example, adults vocalized toward the cat earlier in an interaction and for longer periods, whereas adolescent human beings (11 to 15 years of age) spent the least amount of time in close proximity to the cats and had the least amount of interaction. Gender played some role: women spent more time interacting with cats than men, but this was partly because women in this group were home more. These findings may serve as "norms" for practitioners; variations from these "norms" (e.g., adults working long hours, leaving adolescents home alone with pet cats for long periods) may result in problems. These may be resolved fairly readily with appropriate advising; for example, a practitioner may suggest the adolescent be taught to approach and talk to the cats periodically, rather than to follow them around or ignore them.

Heidenberger[36] also provided insight into how cats and human beings actually interact by surveying 550 German cat owners. Her results illustrate again that cat-cat interactions alone are not sufficient to explain cat behavior in the home and that people are important additional determinants of that behavior. She found that most owners had nonpedigreed domestic shorthair cats (65 per cent), most of which had been neutered (79 per cent). More than half of the households had more than one cat (59 per cent), with an overall average of 2.2 cats per home.

Although the average number of people in the home was similar to that of the number of cats (2.3), only an average of 1.8 of those people actually dealt with the animals; that is, not everyone interacted with the cats on a regular basis.[36] Women tended to take care of the necessary chores such as feeding and caring for the animals while men tended to play with them. Cats were handled (e.g., played with) on average about 2.5 hours per day, although they were alone an average of 6 hours per day. The average cat in this group was restricted to 34 m^2 of space, rather than having the run of the house. They had an average of five resting places (favored spots) and the owner's bed was the most frequently mentioned resting place; no information was provided about sharing of places. Only 14 per cent of cats were allowed outdoors without restriction. Another 29 per cent were allowed out with restrictions on where they could go and for how long. About half of the cats (51 per cent) were reported as liking to play mostly with other cats, whereas about 29 per cent preferred playing with their owner and an additional 18 per cent seemed to prefer both equally. Only a few of the cats were reported to prefer to play with a dog or a child.

Owners complained of having problems with the cats, that is, behaviors they would like to change.[36] Owners differed in what they considered problems. More than 600 responses about problems were related to just four problems: anxiety states (such as running from visitors and hiding, disliking to be touched by owner, fearing children; mentioned for 197 of 1177 cats), scratching on furniture (179), feeding problems (such as eating fast, overeating, continuous seeking and begging for food, or need for special food [128]), and aggression problems (124), with inappropriate elimination running close behind (96).

In general, the family situation and quality of the relationship were related to the frequency of problem responses.[36] Somewhat surprisingly, those without children complained more often about their cats than did those with one to three children, and less surprisingly, people who interacted with their cats for several hours, spread evenly over the day, and experienced owners (who had had at least four cats before) complained less often about problems. Cats kept in groups of two or three or allowed out only rarely or only in good weather were reported as having more problems than others; single cats or cats in large groups and cats allowed out whenever they wanted or at least regularly (two to three times per week or all weekend) had significantly fewer problems. Clearly, cat-cat interactions, human-cat interactions, and owner and cat perceptions play important roles in the overall evaluation of cat behavior in the home.

In addition to these studies, applied animal behavior practitioners have compiled a wealth of data about cat behavior in the home, problems that arise in specific situations, and a variety of treatment and prevention plans based on their practical experiences. Much of this information has been published in brochures and videos,[37] in online website newsletters,[38] or in popular books for the general public.[39,40] However, little has been published as research studies with formal data analysis, which makes it difficult to assess the material or recognize patterns that could be used for treatment. Published material also is scattered, which makes it difficult for other practitioners to access and use when advising clients.

Additional Human-Cat Interactions That Affect Cat Behavior

A number of other important behaviors occur between human beings and cats that affect cat behavior in the home, including providing cats with access to the outdoors, feeding cats, dealing with cat litter, petting cats and other physical contact, and human-cat communication. Allowing cats access to the outdoors has become controversial in the last decade or so, especially in the United States. A number of pressures have resulted in a sharp increase in owner restriction of cats. For example, research suggesting that cats are highly efficient predators with the ability to decimate wild bird populations[41] resulted in the call by many humane organizations,[42] wildlife conservation groups,[43] and ornithological associations[44-46] to ban cats from the outdoors. These conclusions have been tempered[47,48] by newer findings that such decimation has been demonstrated clearly only on island populations, where highly constricted habitat and high density of prey exist and that cat age and home setting (rural versus urban) are important factors that affect hunting (see Chapter 74). However, the belief that cats are a menace has persisted.

Other problems also play a role in owners limiting cat access to the outdoors, including increasing risk to cats from their own predators (raptors and coyotes, especially in Western and New England states); the growing volume of vehicular traffic; com-

plaints by neighbors about roaming cats; an increase in infectious and often lethal diseases (e.g., FIV infections, feline leukemia virus infection, and feline infectious peritonitis); owner fear of zoonoses despite lack of evidence to support common transfer of disease between cats and human beings (including toxoplasmosis); and the growing population of feral cats that could result in increases in cat fights, cat bites, and transfer of disease to household cats that encounter them.[50,51]

Concerns about these issues seem to be having an impact. In a preliminary survey of cat owners in the United States from 1993 to 2003 (mode = 1997) of 256 households with 503 cats (single and two-cat households), Bernstein found that 50 per cent of cats were being kept indoors at all times, a dramatic increase.[51a] Of those allowed outdoors, only 33 per cent were unrestricted, with an additional 15 per cent allowed outdoors with restrictions, such as sitting with owners on decks, being walked on leashes, kept in the yard on a lead, or kept in small fenced-in areas. These findings are similar to those of Heidenberger,[36] who surveyed German cat owners during a similar time period, in which 55 per cent reported that cats were allowed to "run free" in various ways and frequencies, including some restriction outdoors.

These figures are in sharp contrast to those released by the Feline Advisory Bureau[48] (FAB) from a survey of 1853 British cat owners in the early 2000s, in which 75 per cent of cats were allowed out at will during daylight hours, although only one third of these were totally unrestricted. The FAB survey also found that hunting by cats was likely to have much less effect on prey populations than estimated previously[41,43,48]: only about a quarter of cats were said to hunt regularly (determined by direct observation or from prey being brought in), and hunting activity was most prevalent only in young cats, peaking between 4 and 7 years of age and decreasing dramatically in older cats (which were 60 times less likely to hunt than 2-year-olds). Further, cats in rural homes were almost twice as likely to hunt as cats in urban settings, again decreasing the estimates of the number of prey being taken.[43,48]

Missing from this discussion are formal studies of whether cats kept primarily or fully indoors are more prone to develop behavioral and other problems. Aside from the surveys by Heidenberger[36] and FAB,[48] few formal sources of information exist regarding this issue. Both studies found that owners were more likely to complain of problems if cats were kept indoors or only rarely or irregularly allowed outside. In the FAB survey,[48] cats that were not allowed outside were one-and-a-half times more likely to exhibit indoor toileting problems and more than twice as likely to engage in indoor spraying. Applied behavior practitioners and anecdotal sources are additional important sources of information about this issue, especially in providing treatment guidance based on experience. But the information must be sought out.

Although a large literature exists on diet and nutrition aspects of pet cat care, few studies have observed human-cat interactions directly at feeding times, including initiation of the event, coordination, and ending. Because getting food from owners is an important aspect of pet cat behavior, especially if cats are kept indoors, it would seem critical to examine how cats and people manage this interaction, where communication and manipulation by one or both parties may play important roles. Bradshaw and Cook[49] observed the behavior of 36 cats during feeding to gain an overview of cat behavior in this setting and the role of cat personality. Not surprisingly, cats spent much of the premeal period interacting with the owner and using communication signals such as meow, tail-up, and rubbing. Much of the post-meal time was spent grooming, with much less interaction with the owner. Human behaviors were not studied, however, and coordination was not examined.

Another human-cat interaction that affects cat behavior in the home is petting. Although cats allogroom one another and people touch one another, petting is a human-cat interaction in which both parties must find ways to modify species-typical behavior. Both parties seek the interaction and therefore must enjoy it. But few studies have examined directly how the interaction is initiated, maintained, and ended. Instead, various pieces have been examined. Some studies have focused primarily on areas of the body petted most often by human beings or that seem preferred by the cats,[52,53] with some examination of the behaviors cats used to initiate the interaction (Figure 71-3). A group of studies also sought to determine what owners gain emotionally from petting their cats; that is, whether petting provides emotional support for people by elevating their mood as it seems to in human-dog interactions.[54-56] Results indicated that cats seemed to help decrease negative mood but did not seem predictably to put owners in a good mood.[24,54,56] Some information about initiation of petting by both parties also was provided. At least one study dealt with duration of the interaction and found most were less than a minute.[34] Because petting can be a strongly positive or somewhat negative interaction for people (i.e., when it results in cat aggression),[57] more research about this interaction and its affect on cat behavior in the home would be beneficial.

Although much has been written about providing cats with litterboxes (size, shape, type and amount of litter, number and placement of boxes), few formal studies have been performed regarding the ways human beings and cats interact over this issue, and how it affects cat behavior ultimately in the home. Because inappropriate elimination is a major complaint of cat owners and often is given as a reason for relinquishment, studying this issue more directly would seem critical. Also, contact-seeking behavior other than petting (e.g., sleeping with owner,

Figure 71-3. Petting is one of the most common interactions that occur between cats and human beings, but few formal studies of this interspecific activity have been conducted. Although petting often seems to involve areas that are allogroomed commonly by other cats, and hence may resemble cat-cat interactions, some petting activity seems specific to human-cat interaction. Here Tiger is petted on the lower abdomen, an area for which she often solicits petting and during which she remains in place and does not scratch or bite. This area usually is not allogroomed by other cats and usually not favored by most cats during human petting.

sitting on owner's lap, owner picking up cat) has not been studied and also may play an important role in cat behavior, especially in multicat homes in which competition may exist for the resource of "owner attention." Further, although some research has focused on introduction of new cats to cats already occupying a home,[15] little work has been done on problems that involve introduction of new cats to the human beings in the home, or introduction of a new person to the home. Further, almost no one has investigated what occurs when a human being in a home dislikes cats in general or one cat in particular but must deal with them or when a particular cat dislikes a particular person. How cats and people interact may have an impact on how cats interact with each other.

Signaling between owner and cat also could contribute to owner-cat difficulties if communication goes badly, but this subject has not been well studied. A preliminary experimental study indicated that human beings interacting with a strange cat in a neutral room talked to the cat using language similar to child-directed speech and apparently modified their speech to match the perceived comprehension level of the listener.[58] However, no studies have attempted to directly observe human-cat "conversation" in the home, as either or both vocalize to one another in attempts to communicate. None have examined if and how cats may modify their vocalizations when engaging people versus other cats. None have examined whether cats use or modify tail signals during interaction with human beings.

Some studies have examined cat vocalizations directly and attempted to parse them by context to decipher messages or meanings.[13,59-61] A few studies have examined human perception of cat vocalizations, to see if recognizable categories were shared by person and cat (i.e., could human beings classify them into the contexts in which they were given).[61] People were just barely able to classify the calls, being slightly above chance levels. Not surprisingly, experienced owners were somewhat better than those with less experience, but they, too, were only somewhat better than chance. This suggests the calls have low predictive value or people have not learned them well. A related study demonstrated that human beings could classify wild cat and domestic cat vocalizations in emotional terms (e.g., pleasant, unpleasant) and discriminate reliably between them on that basis. These observations suggested that some physical aspects of domestic cat vocalizations (e.g., frequency, sound quality) may have been selected adaptively to elicit positive responses from people.[62]

Sometimes the human-cat relationship goes terribly wrong, which results in behavior problems, abuse of various kinds (see Chapter 73), hoarding, relinquishment, or abandonment. Growth in interest and research in these topics has been explosive in the last decade. Major veterinary societies have suggested strategies, set policy, and formed consortia to investigate these issues further.[63-65]

SUMMARY

Although studies of wild cats and of feral domestic cats can be helpful to predict expectations of cats in the home and management of them, pet cats have a number of different challenges with which to cope. Most important of these are the various constraints imposed by home living and the human-cat interaction itself. Studies of feral cat behavior have provided important background for understanding domestic cat behavior in the home. The few existing formal studies of cat-cat interaction in the home, and many more applied behavior case studies and anecdotes are providing a more direct understanding. Studies of human-cat interaction are beginning to provide an understanding of that aspect of pet cat behavior. Combining information from all of these approaches, such as finding that flexibility in group size and a keen awareness of individual identity and relationships are important aspects of cat behavior, is crucial to a more informed understanding of cat behavior in the home and to providing advice to owners on how to best care for their cats.

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Chapter 72

Euthanasia of Cats in the Animal Shelter Environment

Leslie Sinclair

The word euthanasia is Greek in origin. Taken literally, *eu* + *thanos* means "good death." Some people define euthanasia to apply only to those circumstances in which an animal is in pain and actively suffering; others use the term more expansively to refer to ending the life of an animal for whom no hope exists for a life of good quality, whether because of chronic illness, dangerous behavior, or lack of a suitable home.

Protocols and methods for administering euthanasia are not often presented in the veterinary literature, perhaps because the veterinary profession as a whole prefers to focus on healing, rather than on hastening death. Euthanasia is considered by some to be a technically easy procedure, when in fact a good deal of information is necessary to provide a humane, reliable death for cats, especially for the widely varied population of cats that is presented to most animal sheltering agencies. Improvement of the technical aspects of euthanasia can increase the quality of the euthanasia procedures that veterinarians and animal care and control personnel provide, in addition to raising the confidence and minimizing the distress that may be felt by those who administer it.

How many cats are euthanized annually by animal care and control agencies in the United States? Cats are the most numerous domestic pets in the United States, and surveys estimate that more than 73 million cats are owned.[1] Several national animal organizations have suggested that free-roaming, unowned cats are equally numerous. Although reliable statistics to characterize the admission and euthanasia of cats in our nation's animal shelters are hard to come by, no doubt exists that the number of cats currently euthanized annually is millionfold. This number likely belies the true enormity of the free-roaming and feral cat population in this country. Pockets of the United States still exist where animal control has not even begun to address the feline population, where animal control officers are known as "dog wardens" and no laws, funds, or facilities are available for cats. Whereas these jurisdictions have failed to even address the issue of free-roaming and feral cats, others have recognized the issue but are at a loss as to how to address it. Possible approaches have been characterized as "trap, remove, and euthanize," "trap, remove, and relocate," and "trap, neuter, and return."[2] Regardless of which of these programs is employed, trapping and evaluating any population of cats leads to identification of a greater number of cats that are in need of care, including euthanasia. Obviously, as the management and control of unowned cat populations in communities become more comprehensive and more effective, the number of cats requiring euthanasia will increase.

AN ABSENCE OF VETERINARY FOCUS

Euthanasia is a topic that has not been well addressed in formal veterinary education. Only scant research has been conducted and published on the topic of veterinary attitudes and capabilities regarding euthanasia. Anecdotally, it appears that the curricula of most veterinary schools address no more than the pharmacology of sodium pentobarbital and other anesthetic drugs used in the process of euthanasia, and how to counsel the owner of a pet who is dying, has died, or has been euthanized. Little is taught about other methods of euthanasia that are or have been used for the purpose of euthanasia in animal shelters in the United States (such as carbon monoxide), or about routes of administration of sodium pentobarbital other than intravenous injection. Regardless of this absence of educational focus on the topic of euthanasia, the veterinary community seems to be confident, and the public appears to agree, that veterinarians are the ultimate authorities on the topic of euthanasia of sheltered animals, despite the significant numbers of sheltered animals that are euthanized by nonveterinarians in animal care and control agencies. Like so many other aspects of animal control, laws addressing the topic of euthanasia of sheltered animals vary tremendously from state to state. State veterinary licensing boards and veterinary associations often play significant roles in drafting, developing, and passing these laws, and in administration of them.

For many reasons, shelter euthanasia perhaps is more emotionally difficult than private practice euthanasia. Milani[3] contrasts the two: "Who best can offset the emotional trauma of having to put an animal down: The veterinarian, who, on any given day, treats many animals that will recover and do belong to caring owners, or the shelter workers daily assaulted by far more evidence of often heartbreaking human cruelty and

neglect than human good?" Greater numbers, the terrible condition of some sheltered animals, and the healthy, adoptable condition of others, add an additional measure of grief for those persons who must dictate and administer euthanasia to cats in shelters.

Other obstacles to better instruction in euthanasia topics include veterinarians' perceptions of themselves as healers, and the misperception that the need for euthanasia of unwanted and surplus animals will soon come to an end in our society. Much progress has been made over the past 2 to 3 decades in examination of our methods to deal with unwanted or surplus animals, and several communities have committed themselves publicly to the concept of ending euthanasia for these reasons. Perhaps these movements have suggested to the veterinary community that euthanasia of animals in animal shelters soon will be no longer necessary, giving them an opportunity to avoid the topic altogether.

Euthanasia will, however, always be a necessary aspect of animal sheltering, because animal shelters take in animals that can be made medically and behaviorally sound for adoption and those that are unsocialized and/or severely injured or ill, and for whom euthanasia is the kindest option available. Certainly the need for euthanasia will diminish with time, but expecting its need to be eliminated entirely is unrealistic, and a disservice to those animals that must be euthanized in the present and the future.

WHO EUTHANIZES?

Who euthanizes cats in the United States? No statistics or records tell us how many animals are euthanized by private practitioners. Statistical accounts of the numbers of cats euthanized in animal shelters in the United States have been examined more thoroughly but are just as hard to come by. However, most of the millions of sheltered cats that are euthanized in animal shelters are euthanized by nonveterinarian shelter workers.

Training of euthanasia technicians, as these workers are called, varies from state to state and agency to agency. Many states have created specific guidelines for the training of euthanasia technicians, and some of these require that those who perform euthanasia become "certified" to do so by attending approved training and submitting an application that documents their identity, training, and experience. Training requirements range from minimal to extensive and include classroom lecture, hands-on training, and/or on-the-job training. Recertification may or may not be required on an ongoing basis. The laws of some states appear to intend that training ensures animals are euthanized in a humane, technically proficient manner, whereas others appear to intend only that the use of controlled substances used in the euthanasia process be monitored carefully. Several states have no laws regarding the euthanasia of sheltered animals.

State laws also govern whether and how shelter personnel may gain access to sodium pentobarbital and other drugs used in the euthanasia process. Sedatives, tranquilizers, and anesthetic drugs often are used before administration of euthanasia agents to improve the quality of euthanasia and to enhance the safety of those performing the procedure. Acepromazine, xylazine, ketamine, and tiletamine-zolazepam are common drug choices. Each of these drugs can be administered by a route other than intravenously (IV), which diminishes or eliminates the need to restrain the conscious animal manually for venipuncture.

Because all of these are "legend drugs" (approved by the Food and Drug Administration "for use by or on the order of a licensed veterinarian") and because some of them are controlled substances, many shelters have difficulty obtaining and using them. Traditionally, veterinarians have not played a significant role in the sheltering of animals, and many sheltering agencies are either unable to secure veterinary participation or are loathe to accept it because of previous conflicts. Obtaining drugs, especially controlled substances, from a practitioner who is not employed by the shelter is a situation fraught with concern and liability for both the practitioner and sheltering agency. For this reason, at least 26 states have provided shelters with the means to acquire sodium pentobarbital directly for euthanasia purposes,[4] but shelters in the remaining states must acquire it indirectly, from a licensed veterinarian. The availability of sedatives, tranquilizers, and anesthetics is crucial to a shelter's ability to provide a peaceful, safe ending to a cat's life, yet all shelters must obtain these drugs indirectly, through a cooperative veterinarian who is employed by the shelter or is willing to provide them to the shelter.

EUTHANASIA METHODS

Our knowledge of euthanasia is organic, changing and evolving with time and as new information becomes available. Many methods of ending the lives of animals, not all of them meeting the definition of euthanasia, have been used by animal care and control staff and by veterinarians over the years. Methods once thought to be ideal, such as administration of carbon dioxide, have since been discarded when a better alternative became available. Carbon monoxide is a method that found favor as a means of ending the lives of sheltered animals during the latter part of the last century, but it is becoming obsolete quickly because of public sentiment (although it is still widely used in the United States). Methods often are discarded because of the safety risk they pose to the operators as much as because of their effect on the animals who are being euthanized.

The intention of euthanasia is to provide a painless and humane death for a cat that is suffering, homeless, deemed dangerous, or otherwise cannot be expected to live a life of good quality. Many methods for ending the lives of cats and other species purposely have been used and investigated. The American Veterinary Medical Association has convened a panel of experts on six occasions, referred to as the AVMA Panel on Euthanasia, and charged them with the task of reviewing and commenting on methods for euthanasia. Each panel has published a report of its findings[5-10]; the first report was published in 1963 and the most recent in 2001.

The reports of the AVMA Panel on Euthanasia have been used widely as references by those who want to select the best possible methods of euthanasia for different populations of animals. The *2000 Report of the AVMA Panel on Euthanasia* addresses the euthanasia of dogs and cats in private veterinary hospitals, animal care and control facilities, and research facilities, in addition to poikilothermic, aquatic, and fur-bearing animals, horses, and wildlife.[10] The report does not address predator control and depopulation or slaughter of animals for food. Because of the wide range of situations and animals discussed by the report, its authors caution that its content is intended to serve as a guideline requiring the use of profes-

sional judgment for application to the various settings where animals must be euthanized. Therefore, although the report provides a wealth of information about euthanasia, it cannot be used without careful consideration of whether it applies accurately to the needs of the individual animal that is presented for euthanasia.

Of all the available methods for performing euthanasia, really only three possible mechanisms exist: hypoxia, physical disruption of the central nervous system, or pharmacological disruption of the central nervous system. Exposure to high concentrations of carbon monoxide is an example of a euthanasia method that acts by causing hypoxia. Carbon monoxide replaces oxygen on red blood cells and prevents it from reaching the brain and other body tissues. Gunshot (when performed properly so that ammunition of an appropriate caliber rapidly enters the brain) is an example of physical disruption of the central nervous system. Death occurs because the portions of the brain that control cardiac and respiratory activity are destroyed.

Pharmacological disruption of the activity of the central nervous system is accomplished most commonly using inhalant anesthetics or barbituric acid derivatives (usually sodium pentobarbital). These agents depress the central nervous system, which in turn leads to death of the portions of the brain that control cardiac and respiratory activity. The central nervous system is depressed gradually as the animal experiences the five stages of anesthesia (Table 72-1). With proper administration, inhalant anesthetics and sodium pentobarbital result in the animal reaching the fifth stage of anesthesia, at which point death occurs because of depression of the respiratory system followed by cardiac arrest.

Ether, methoxyflurane, halothane, isoflurane, sevoflurane, desflurane, and enflurane are the inhalant anesthetics that have been used for euthanasia. The pros and cons of each of these agents are discussed in the *2000 Report of the AVMA Panel on Euthanasia.*[10] Halothane, which induces anesthesia smoothly and rapidly, is considered the agent of choice for this purpose, although other agents also are acceptable. Nitrous oxide can be added to speed the onset of anesthesia. Used alone, it will cause death by hypoxia but has no anesthetic properties, and the animal may become distressed (because of the feeling of suffocation caused by the hypoxia) before unconsciousness. Therefore nitrous oxide alone is not an appropriate euthanasia agent.

The use of anesthetic gases as euthanasia agents is not common and usually is reserved for cases in which an acceptable route for administration of sodium pentobarbital is not readily available. In most cases, the anesthetic is combined with oxygen and administered by means of an induction chamber. The duration of the procedure may be lengthy; the animal must inhale and absorb enough of the gas to advance through all five stages of anesthesia. Evidence exists that animals under 16 weeks of age are resistant to hypoxia, and because all inhalant gases eventually cause death resulting from hypoxia, it has been recommended that inhalant gases be used only to induce anesthesia, followed by some other method of euthanasia.[10] If anesthetic gases alone are used to euthanize young animals, special care should be taken to verify that death has occurred.

Table 72-1 | **The Five Stages of Anesthesia and Euthanasia**

Stage I: Sedation
Stage II: Involuntary excitement
Stage III: Light anesthesia
Stage IV: Deep anesthesia
Stage V: Apnea (respiratory arrest) followed by cardiac arrest

Sodium Pentobarbital Euthanasia of Cats

By far, the most common method for administering euthanasia is by injection of sodium pentobarbital, also known as pentobarbital sodium and pentobarbitone. When administered intravenously, sodium pentobarbital causes an animal to advance through all five stages of anesthesia in swift succession, resulting in rapid unconsciousness and death. Unadulterated sodium pentobarbital is a Class II controlled substance. Several preparations containing sodium pentobarbital and the anticonvulsant drug phenytoin, which is cardiotoxic, also are available (Table 72-2). The purpose of adding phenytoin is twofold: it enhances cardiac arrest and it diminishes the potential for human abuse of sodium pentobarbital. This combination of sodium pentobarbital and phenytoin therefore is a Class III controlled substance and is more readily available to veterinarians and animal shelters for euthanasia. Although sodium pentobarbital-phenytoin combinations are not approved for use in cats, they are used widely by veterinarians to euthanize cats in private practice situations.

A third combination, sodium pentobarbital plus lidocaine, has been marketed previously and is expected to be available again at some time in the future, after further evaluation by the Food and Drug Administration. Lidocaine, like phenytoin, has an effect on the function of the heart and is cardiotoxic at high doses. The addition of lidocaine to sodium pentobarbital has two additional purposes: it decreases the discomfort that occurs when sodium pentobarbital is accidentally injected perivascularly, and it diminishes the abuse potential of a euthanasia solution, making the combination a Class III controlled substance. Sodium pentobarbital-lidocaine combinations also have been shown to reduce the occurrence of the "agonal gasp" that is exhibited by many dogs and cats during euthanasia with sodium pentobarbital alone.[11]

Determining the best route of administration of sodium pentobarbital is crucial to providing euthanasia. The route chosen depends on many factors, including the cat's behavior, the degree of injury or illness affecting him, the skill and comfort

Table 72-2 | **Sodium Pentobarbital Formulations***

CLASS	MANUFACTURER	CONCENTRATION
II		
Sleepaway	Fort Dodge	260 mg/ml
Euthanasia-6	Anthony	390 mg/ml
Euthanasia Solution	Vet-Labs	324 mg/ml
Fatal Plus	Vortech	390 mg/ml
III		
Beuthanasia-D Special	Schering	390 mg/ml (SP) + 50 mg/ml (phenytoin)
Sold as Euthasol	Delmarva	390 mg/ml (SP) + 50 mg/ml (phenytoin)

*Many sodium pentobarbital formulations have been made available by various manufacturers. This list includes the formulations used most commonly, but may not be comprehensive.

of the person administering euthanasia as well as of those who are assisting, and the formulation of sodium pentobarbital that is being used. Sodium pentobarbital euthanasia formulations work best when injected intravenously; once in the vein, sodium pentobarbital is transported quickly to the heart and then to the brain, its primary site of action. Information regarding the intraperitoneal administration of unadulterated (Class II) sodium pentobarbital solution to cats has been published. The *2000 Report of the AVMA Panel on Euthanasia* acknowledges that intraperitoneal injection of a nonirritating euthanasia agent is acceptable when intravenous administration is impractical or impossible. The method is used widely in animal shelters in the United States for euthanasia of cats, kittens, and puppies. (Anecdotal evidence suggests that dogs to which sodium pentobarbital is administered by the intraperitoneal route tend to struggle to right themselves as they experience the involuntary excitement stage of anesthesia [stage II], although no formal report of the use of this method in dogs has been made.) It is favored particularly by the animal shelter community as a method for providing a humane death for feral, fearful, or fractious cats, especially in the absence of availability of other drugs that might provide chemical restraint or sedation. Most cats and kittens, however, usually advance smoothly through all five stages of anesthesia within 15 to 30 minutes after intraperitoneal administration, especially when they are placed in a warm, dark, quiet area during induction.

Concern has been expressed that, when sodium pentobarbital-phenytoin combinations are administered by the intraperitoneal method, phenytoin may exert its effect on the heart before the sodium pentobarbital component has caused unconsciousness and that this effect may cause pain.[10] The *2000 Report of the AVMA Panel on Euthanasia* states that the pharmacological properties and recommended use of sodium pentobarbital-phenytoin combinations are interchangeable with those of pure barbituric acid derivatives but does not address the question directly of administering such a combination by the intraperitoneal route. Until more information is available about the absorption rates of these two drugs from the peritoneal cavity, sodium pentobarbital-phenytoin combinations should not be used for intraperitoneal administration. For this reason, and because sodium pentobarbital-phenytoin combination formulations are not approved for use in cats, Class II formulations are a better choice for euthanasia of sheltered cats. This creates a significant burden for shelters who euthanize cats in states that do not allow sheltering agencies direct access to sodium pentobarbital, however, because they must develop a working relationship with a veterinarian willing to provide them with a more controlled version of sodium pentobarbital.

Most formulations of sodium pentobarbital contain 390 mg of sodium pentobarbital ("6 grains") per milliliter. The manufacturer's suggested dosage for both intravenous and intraperitoneal administration should be consulted; most formulations are administered at a dose of 1 ml per 4.54 kg (10 lb) of body weight for intravenous administration. Most manufacturers of sodium pentobarbital formulations do not provide a dosage for intraperitoneal administration of their product. A dose of 3 ml per 4.54 kg body weight for cats was suggested in a 1990 publication[13] and revised to 2 ml per 4.54 kg of body weight in a later publication by the same author.[14] Some formulations have different concentrations of active ingredient, another reason for consulting manufacturers' guidelines.

Performing an accurate intracardiac injection is difficult and unpredictable; therefore intracardiac injection of sodium pentobarbital is considered appropriate only when performed on a heavily sedated, anesthetized, or comatose animal.[10] For these reasons, I do not recommend the intracardiac route for administration of sodium pentobarbital to cats. Intravenous injection is more accurate and more suitable for use in an environment in which it may be difficult to assess the degree of anesthesia accurately to which a cat has been induced.

A method for intrahepatic administration of sodium pentobarbital in cats was first presented in 1990,[13] then revised in 1996.[14] Because of the acidic nature of sodium pentobarbital, injection into subcutaneous tissues or muscle is painful. Slow absorption from those sites also results in slow and unpredictable advancement through the five stages of anesthesia. For these reasons, sodium pentobarbital should never be injected subcutaneously or intramuscularly. Likewise, injections into the lungs, thoracic cavity, kidneys, spleen, and spinal fluid are considered inappropriate methods of administration.[10] Oral administration of sodium pentobarbital to cats has been suggested, and at least one agency has reported success at enticing fasted cats to ingest the drug when it is mixed with canned tuna packed in oil.

Chemical Restraint

The use of sedative, tranquilizer, and anesthetic agents before euthanasia often is crucial to providing a safe, peaceful death for a cat. The drugs used most commonly for this purpose are the tranquilizer acepromazine, the sedative xylazine, and the anesthetics ketamine and tiletamine-zolazepam, both of which are controlled substances. Protocols for administering these drugs, either alone or in combinations, have been published.

Physical Restraint

Thorough knowledge of appropriate physical restraint and capture techniques is equally crucial to quality euthanasia. Euthanasia technicians must be skilled at handling cats and able to avail themselves of necessary equipment if a cat's behavior makes it difficult to handle or restrain him. Many devices, including squeeze cages and nets, are available for the purpose of restraining a cat for intramuscular injection of a pre-euthanasia drug. Proper training in the humane use of such equipment is necessary.

Final Care

A final step in the euthanasia process is that of verifying death of the animal. No single method exists for verification of death immediately after it occurs; a combination of observations is recommended and is most reliable. The corneal reflex and the femoral pulse should be absent. No signs or auscultable sounds of respiration should be present. The heartbeat should be neither palpable nor auscultable. Mucous membranes should be pale or cyanotic; the color of the gums, conjunctiva, penis, and vulva may be examined. Rigor mortis, when it occurs, is the most reliable sign of death; it usually develops within a few hours after death. Rigor mortis may fail to develop in juvenile animals or in animals that are elderly or severely debilitated. Hypothermia at the time of death may slow the onset of rigor mortis, and hyperthermia may speed its appearance. When

doubt exists as to whether death has occurred, the animal's body should be set aside in a safe place and should be reexamined periodically until death has been absolutely verified.

Shelters typically dispose of the bodies of the cats they euthanize in one of three ways: cremation, landfill, and rendering. Each of these methods has significant environmental and aesthetic drawbacks, and agencies must decide on a case-by-case basis which method is best for their situation.

Personal Safety

Myriad personal safety issues accompany the process of feline euthanasia. Cats are the domestic species diagnosed most commonly with rabies in the United States,[15] and preexposure prophylaxis is a necessity for anyone who works routinely with cats who are unvaccinated or of unknown vaccine status. Plague is a very real concern for anyone who works with cats in northern New Mexico, northern Arizona, southern Colorado, California, southern Oregon, and far western Nevada, and with any cat who has been transported from these areas. Endoparasites and ectoparasites of cats can be transmitted to human beings or act as vectors of disease.

Proper application of appropriate physical and chemical restraint methods, in addition to practical knowledge of cat behavior in a shelter environment, is crucial to minimize or prevent bites and scratches to those performing euthanasia of cats. Many of the safety hazards associated with performing euthanasia of cats in a shelter environment can be avoided with adequate training, access to and use of appropriate physical and chemical restraint methods (and the drugs and equipment necessary to employ them), mindful hygiene (particularly frequent, thorough handwashing), and control of the parasites that cats bring with them to the shelter.

PERSONAL RESPONSES TO EUTHANASIA

A final hazard that euthanasia poses to those who deal with cats is the emotional toll it wreaks. Personnel who euthanize cats in animal care and control agencies have reported feelings of anger, guilt, frustration, and sadness associated with the task, in addition to physical ailments and alienation from persons not associated with animal euthanasia.[16,17] Negative coping strategies such as excessive smoking and alcohol use, illicit drug use, uncontrolled anger, overeating, and withdrawal may be the result of euthanasia stress. Positive coping strategies such as healthy eating and regular exercise, maintenance of quality relationships outside the shelter, and seeking professional counseling when needed can help euthanasia technicians avoid or minimize the stress of performing euthanasia.

CONCLUSION

Much has been said, and has yet to be debated, about when and why cats may or may not need to be euthanized by animal care and control agencies. Euthanasia of feral cats may be the only choice if the cats are sick or injured, are living in a place where they cannot stay or that is hazardous, or cannot be placed in ongoing care.[2] Trap, neuter, and return programs advocate "non-lethal" control of feral cat populations, yet any well-run program includes provisions for removing socialized cats from free-roaming populations and offering them for adoption, not always a successful scenario. These programs also allow for the identification and isolation of cats with significant injuries or illness, including feline leukemia virus, feline immunodeficiency virus, rabies, plague, and others. The argument is futile that circumstances always will exist that dictate the euthanasia of cats by animal sheltering organizations. The goal must be to enhance the quality of death provided for those animals when it becomes necessary. Despite the desire of most veterinary professionals to focus on the healing aspects of veterinary medicine, euthanasia is an important component of patient care. Euthanasia proficiency, on the part of euthanasia technicians and of the veterinarians in their community, ensures that communities are providing the most appropriate and humane means of death possible to cats for which it becomes necessary.

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Chapter 73

Cruelty Toward Cats

Leslie Sinclair and Randall Lockwood

Of all the species that have been domesticated, cats historically have been subjected to the widest diversity of treatment by human beings. They have been worshipped as gods and reviled as devils, coddled and pampered, and abandoned and abused. Our treatment of cats likewise has created a range of problems for veterinary professionals concerned with their care, from dealing with problems of obesity and overindulgence to tending to the needs of animals that have been neglected, intentionally harmed, and even tortured.

Many factors contribute to cruelty toward cats, one of which is their ubiquity. An estimated 77 million pet cats live in the United States. Nearly half of all cat-owning households have more than one cat. Unowned, loosely owned, free-roaming, and feral cats are equally abundant; most animal welfare and protection organizations estimate an additional 70 million or more of these cats live in this country.

Most authorities consider the cat to be among the most recent animals to be domesticated, with its origins in Egypt.[1,2] No remains of cats exist from prehistoric Egypt or the Old Kingdom (2686-2181 BC). Pictorial representations of cats that clearly are domesticated appear at the time of the fifth dynasty (c. 2600 BC), and from the New Kingdom onward (from 1567 BC) paintings and statues of cats become increasingly common in Egypt.[3]

Serpell[4] notes that the role of cats in the Egyptian pantheon was complex and confusing. Male cats were associated with the sun god, Ra. Cats and lionesses also were linked to the warlike goddess Sekmet. The primary association was with the cat goddess Bastet, a symbol of fertility, fecundity, and motherhood, who also was associated with the moon and menstrual cycles. The prominence of cat cults did not develop until the twenty-second dynasty (c. 950 BC) when the capital became Bubastis, home of the cult of Bastet, and the local cat goddess became the official deity for the kingdom. The view of reverence for cats in Egypt comes almost entirely from the writings of Herodotus about 450 BC. He describes his visit to the temples in Bubastis and the various practices surrounding the cult, including the harsh penalties for injuring or killing cats:

"When a man has killed one of the sacred animals if he did it with malice prepense, he is punished with death, if unwittingly, he has to pay such a fine as the priests choose to impose (Bk II, Ch. 65)."[2]

Later in the same volume Herodotus details the reverence with which deceased cats are embalmed and entombed. Archeologists in the nineteenth century recovered mummified remains of hundreds of thousands of cats from this period. Ironically, this collection of remains provides the first evidence of what may be considered "ritualistic abuse" of cats. The remains consist primarily of young cats, most with radiographically apparent displaced vertebrae (broken necks), which suggests they were bred intentionally for the purpose of creating mummified votives.

The export of cats from Egypt was illegal, so the introduction of the domestic cat into Europe and Asia did not begin until several hundred years after the peak period of the cult of Bastet, finally becoming widespread by the tenth century.[1] The spread of Christianity brought with it what Serpell[5] describes as "extreme ruthlessness in suppressing unorthodox beliefs and in extirpating all traces of earlier pre-Christian religions." Because cats often were central to many of these belief systems, from the cult of Bastet to the worship of the Norse goddess Freya, they became a convenient target for the demonization of all things non-Christian and the focus of myriad forms of abuse intended to drive out and destroy the devil. Cats also were transformed from a symbol of grace, fertility, and maternal care to one of bewitching sexuality and lasciviousness, an association that continues to affect public interpretation and behavior and serves as a justification for continuing abuse.

Conditions did not improve for cats until the mid-nineteenth century. In the United Kingdom, cats were not afforded protection of anticruelty laws until the 1835 revisions of the 1822 animal welfare legislation protecting livestock, which extended the protections to domestic pets.[6] The annual report of the Royal Society for the Prevention of Cruelty to Animals (RSPCA) detailed the animal cruelty cases investigated and prosecuted under these laws. The majority of cases continued to involve maltreatment of livestock and draft animals, but proponents of companion animal welfare recognized growing concern about the abuse of dogs and cats. From 1857 to 1860, dogs and cats accounted for only 2 per cent of cruelty convic-

tions, although 13 per cent of the RSPCA's reports to the public focused on dog and cat cruelty cases.

In France, the first success of the emerging animal protection movement was the Grammont Law of 1850, which prohibited public abuse of animals. Grammont, a retired cavalry officer, promoted the legislation in part because "the spectacle of suffering encourages cruelty . . . the child accustomed to bloody pastimes or witnessing cruelty will become a dangerous man."[7]

The historical ambivalence of many cultures toward cats has continued into the twentieth and twenty-first centuries. In the 1980s, cats became the most abundant species (excluding aquarium fish) in American homes, a trend that has continued.[8] Although the number of homes that contain dogs is greater than those that contain cats, more people own multiple cats than they do multiple dogs. Despite this popularity, cats have not achieved equal status with dogs as companion animals. Many areas of the United States still do not have laws or agencies charged with the control and protection of cats, despite the presence of agencies, laws, and "dog wardens" to care for dogs. A continuing stream of "humorous" material promotes or at least makes light of cat abuse that has no parallel in the canine world. Popular books such as *How to Kill Your Girlfriend's Cat* and *101 Uses for a Dead Cat* have several sequels, as do the video games "Cat Hunter" and "Cat Blaster." A significant proportion of the population express active antipathy toward cats: Kellert and Berry[9] found that 17.4 per cent of people surveyed expressed some dislike of cats compared with 2.6 per cent who disliked dogs.

Despite their relatively small size and fragility, cats have a reputation as survivors, perhaps in part because of the speed, agility, quick reflexes, and other adaptations that allow them to survive situations than would be likely to kill a human being or dog. Although this kind of resilience may have contributed to the perception of the "invulnerability" of cats, Tabor[10] attributes the specific notion that cats have "nine lives" to distortions of a statement in about 1560 by Baldwin in "Beware the Cat" who wrote that "it was permitted for a witch to take her cattes body nine times." At the same time, this resilience is to blame for a great deal of feline suffering. Morris[11] notes, "Because cats can survive when thrown out and abandoned, it makes it easier for people to do just that."

Cruelty to animals in general has long been associated with an increased risk for involvement in criminal and antisocial behavior.[12-15] Cruelty to cats has been associated specifically with future tendencies toward violence in a number of quantitative and anecdotal accounts.

Felthous[16] provides case histories of violent crimes involving prior acts of cruelty to animals, including one in which a man shot his cat, believing it to be gaining control of him, several days before shooting his wife. Building on these earlier surveys, Felthous and Kellert[17] provided a systematic review of the choice of animals for abuse based on interviews with 84 prisoners in two penitentiaries. The greatest variety of cruelties had been inflicted on cats (33 different forms of abuse were described) and most subjects who had abused cats used several different methods. Cats were the most frequent targets across all forms of abuse and were the predominant victims in cases involving burning, breaking of bones, or being thrown from a height. They conclude: "physical features of cats render them suitable for some specific methods of abuse. Cats have long flexible tails that can be joined together. Fur burns. Their bones are easily broken. Cats are small enough to be carried about and dropped from heights" (p. 231). They note that these qualities are not unique to cats and suggest that cultural patterns and sexual symbolism contribute to the selection of cats for abuse by violent offenders.

The selection of cats as the object of abuse is more than just a result of their availability. Their physical, behavioral, and symbolic attributes often make them the target of choice for those who are, or who are destined to become, perpetrators of violence against people. This makes detecting, reporting, and responding to acts of cruelty against cats an even more pressing concern.

IMPLICATIONS FOR VETERINARY PROFESSIONALS

Cruelty to cats is a widespread phenomenon with serious implications for animal welfare and for potential identification of situations in which children, spouses, the elderly, and others may be at risk. Given the popularity of cats as companion animals, veterinary practitioners are likely to encounter cats that have been victims of neglect, abuse, or even torture. Myriad reasons exist for the veterinary community to involve itself with recognition of, and response to, cruelty toward all species of animals, and cats in particular. Traditionally, the veterinary community has not played an overreaching role in recognition and response to animal cruelty. Obstacles to veterinary involvement include lack of understanding of the typology, nature, and origins of animal cruelty; lack of correlative scientific and clinical literature; concerns about confidentiality and liability; concerns about personal safety and community reputation; time commitment; lack of knowledge about the connection of animal cruelty to human violence; lack of knowledge about the legal process; and lack of ability to shoulder the financial commitment that is the inevitable result of becoming involved in any legal proceedings.

But veterinary interest in, and emphasis on, animal cruelty detection and investigation is growing rapidly. Societal interest in prosecution and punishment of cruel acts against animals has increased tremendously in the past 2 decades, resulting in more laws against, and stiffer punishments for, such acts. Now that animal cruelty cases are no longer simple misdemeanor offenses largely ignored by the legal system because of their paltry nature, veterinarians are being called on to offer expert testimony in felony level cases. The science of forensic veterinary medicine is not prepared for this responsibility, but efforts such as the inclusion of this chapter in mainstream veterinary textbooks are beginning to bridge the gap between what society expects of veterinarians in such cases and what veterinarians are prepared to offer.

The American Veterinary Medical Association (AVMA) has addressed, in its Statement on Animal Welfare (1994), the need for veterinarians to *report* suspected cases of animal cruelty but has not gone so far as to suggest that veterinarians should play a more active role in the investigation and prosecution of such acts:

> The AVMA recognizes that veterinarians may have occasion to observe cases of cruelty to animals, animal abuse, or animal neglect as defined by state law or local ordinances. When these observations occur, the AVMA considers it the responsibility of the

veterinarian to report such cases to the appropriate authorities. Such disclosures may be necessary to protect the health and welfare of animals and people.[18]

Veterinarians who are naive responders to acts of animal cruelty must first educate themselves: What is animal cruelty? Who has the authority for addressing incidents? How might a veterinarian become involved in such a case? What are the veterinarian's responsibilities?

DEFINITION OF ANIMAL CRUELTY

What is animal cruelty? *Neglect* has been defined as the unintentional lack of care that comes from ignorance, *abuse* as more willful knowledge of failing to provide care or the awareness of doing something harmful, and *cruelty* as the deliberate infliction of pain on an animal from which the abuser derives enjoyment or amusement.[19] The terms themselves are abused and have been overused to describe a broad range of behaviors and motivational states.[20] Early animal cruelty laws in the United States were based on the premise that animals of commercial value (such as draft horses) should be protected from cruel acts because of the damage done to the owner's property, and the resultant possible loss of income from the use of that animal. Two primary types of laws exist in the United States[21]: *Criminal law* defines the boundaries of the relationship between an individual and society. Acts that are harmful to people and those that disrupt the order of society are criminal acts, classified as either misdemeanor or felony offenses depending on society's view of the severity of the offense. In the United States, violations are addressed against the perpetrator through a district or state attorney at the local and state level, or the United States Attorney General at the national level. *Civil law* pertains to the relationships among individuals within a society, and two types exist: contract law and tort law. Contract law deals with duties established by individuals as the result of contractual agreements. Tort law deals with duties of individuals toward other people as established by law. Tort laws cover such circumstances as negligence, product liability, libel and slander, invasion of privacy, assault, and nuisance.

Acts of animal cruelty fall primarily under criminal laws. Only 2 decades ago, most instances of animal cruelty were misdemeanor offenses, often considered unworthy of the effort required to pursue them. Today, 27 states include felony penalty provisions for one form or another of animal abuse or neglect in their statutes, and federal laws address some specific forms of animal cruelty, such as animal fighting and harm to a police dog or horse. Animal cruelty statutes in every state have established certain duties and responsibilities for owners toward animals in their care and also prohibit certain acts. All statutes have at least broad language prohibiting deliberate acts of cruelty and inflicting unnecessary physical pain and suffering. Provisions often demand adequate food, shelter, and/or necessary veterinary care, relief of suffering, or conversely, prohibit deprivation of food, water, or shelter. Much requires interpretation, particularly what exactly constitutes "unnecessary pain and suffering."[22]

Unfortunately, the variety of crimes against animals is as limitless as the human imagination. Intentional abuse of cats takes the form of burning, poisoning, blunt and sharp force trauma, gunshot, drowning, asphyxiation, and sexual assault. Our society widely accepts "loose ownership" and abandonment of cats. Recognized neglect of cats occurs primarily in situations in which the cat is confined in such a manner that the person confining the cat can be reasonably expected to be responsible for providing for the cat's food, water, shelter, and care of injuries and health problems. Hoarding of cats, in which the cats are confined so that they cannot roam and forage for themselves, is a phenomenon well-recognized within the animal sheltering community.

AUTHORITY FOR ADDRESSING CASES OF ANIMAL CRUELTY

Much of the veterinary community's hesitation to respond to acts of animal cruelty is the result of confusion about whose responsibility such a response is. Veterinarians are considered to be experts in all matters relating to animals. Therefore they often believe mistakenly they must assume the roles of investigator, prosecutor, judge, and jury with respect to animal cruelty cases; however, a report of suspected neglect or abuse is only the first step in a case. Other experts and legal authorities play roles just as important in determining the true circumstances of an animal's injured or diseased condition. A veterinarian is one member of a team of professionals involved in cases of cruelty, abuse, and neglect.[22]

Determining to whom a report should be made sometimes can be a frustrating and confusing process. In each jurisdiction, the answer may be different. Some communities may have appointed animal control officers or humane investigators. Some independent agencies (usually nonprofit animal sheltering organizations) investigate complaints from the public, without any legal authority, yet are successful because of cooperative relationships with authorities and with their prosecutor's office. Most animal cruelty laws are state statutes, and in the absence of any other appointed authority, local law enforcement officers are responsible for enforcing them, although they may not be aware of, educated about, or motivated to do that.

A report of suspected abuse or cruelty rarely leads to prosecution and conviction of the perpetrator. Particularly in cases of neglect in which the animal's life is not immediately threatened, a report to an investigative agency allows that agency the opportunity to educate the pet owner formally about their legal responsibility to care for the animal. Other cases stall because of lack of evidence or corroborating witnesses.

Taking an animal into custody against the owner's wishes may involve a variety of administrative, civil, or criminal procedures that will be unique in each state. Therefore, the specifics of the process and the agency with the statutory authority to seize a neglected animal may vary considerably.[23]

Routes of Involvement

Whether or not they wish to, most veterinarians become involved in an animal cruelty case at some time during their careers. Of 110 Massachusetts veterinarians surveyed in 1999, most (79 per cent) reported having seen at least one patient during their careers with injuries they suspected were inflicted by the client or another member of the household. Nearly half (47 per cent) were positive or very sure they had seen injuries that were deliberate, and one third (34 per cent) indicated that a client admitted to causing injury to their pet. Most (81 per cent) reported they had observed neglected or abused animals in their community.[24]

A veterinarian may become involved in an animal cruelty case when a client-owned animal has been abused or neglected by their owner. Although this may seem improbable, some perpetrators feel remorse after an incident or agree to accompany a spouse or other family member who seeks veterinary care for the animal. Other routes by which a veterinarian may become involved are when a client's animal has been abused or neglected by someone other than the owner, when animals owned by a nonclient are abused or neglected by their owner, or when unowned animals are abused.[25] These last two cases usually involve an investigative agency that contacts the veterinarian to assist with an investigation.

Veterinarian Responsibilities

The AVMA has suggested that a veterinarian's responsibility is to report suspected animal cruelty; however, much more is required ethically and legally of a veterinarian who is a witness to evidence of a criminal action. Many veterinarians hesitate to report suspected cruelty because of the belief that their relationship with the animal's owner is confidential and that they will be liable for a breach of confidentiality if they provide information to investigative authorities.

Like so many other aspects of addressing animal cruelty, such confidentiality and liability vary significantly from state to state. Some states have indicated specific circumstances in which confidentiality requirements are waived explicitly to protect public or animal health. Most states allow for reporting in cases in which the welfare of the animal and/or other animals or persons in the household is at risk of abuse or neglect. Additionally, many states provide reporters with protection from civil liability if the report is made in good faith, even if charges against the suspected perpetrator are never acted upon. Statutes and rules regarding veterinary confidentiality and liability are found, in most cases, within a state's veterinary practice act.

Once an act of animal cruelty is suspected, a veterinarian's participation in the investigation often is crucial, even more so now that our society has deemed these cases of felony importance. Legally, as witnesses to evidence of a criminal act, veterinarians become involved in the investigation and prosecution efforts, voluntarily or not, and their involvement is subject to subpoena by the prosecutor.

Will veterinarians involved in the response to an act of animal cruelty be compensated financially for their time? Much depends on how the veterinarian became involved in the case. In most cases, the answer is no, and the veterinarian's participation is an ethical or legal obligation. Veterinarians who work for an organization that investigates animal cruelty or for a municipal agency whose responsibility is to enforce animal cruelty statutes are compensated routinely as a matter of course, because their duties likely include participating in cruelty investigations. The best method for minimizing the financial burden of participation in an animal cruelty case is to work in cooperation with the prosecutor, who can, within reason, determine how much time and effort the veterinarian, as a witness to the evidence of the crime, must contribute.

Forensic Examination

When veterinarians become involved in the investigation of an act of animal cruelty, they move out of the realm of general veterinary practice and into that of forensic veterinary medicine. The phrase "forensic veterinary medicine" may be applied to any situation in which both medical and legal analysis of an animal's condition and the surrounding circumstances is necessary. As in the field of human medicine, however, the term forensic is used more commonly to refer to the investigation of the injury, illness, or death of an animal because of possible criminal action.

The forensic examination of an animal, whether living or deceased, varies significantly from diagnostic examination. The examiner must determine the animal's ailment and the method and mechanism by which an injury or illness occurred.

Many of the disciplines of human forensic science may be used to investigate animal forensic cases. Reconstruction of the crime, as a mental or physical exercise, may provide useful clues about how the incident occurred and who may have been involved. Blood stain pattern analysis is a highly evolved science and its most basic tenets may be useful for evaluation of the evidence of criminal animal cruelty. Projectile recovery and analysis are other techniques that may be borrowed from the human field. Because toxicological analysis is a well-developed veterinary field, poisoning perhaps is the easiest animal cruelty crime to document accurately, although a significant difference exists between proving an animal has been poisoned and proving who administered the poison.

Photographic and radiographic analysis of criminal evidence also is highly useful in animal cruelty cases. Photographic documentation allows evidence to be portrayed carefully at a later date. Radiographs may be used to detect and diagnose injuries, to identify the number and site of projectiles in a victim, and to document evidence. Forensic entomology is another "criminalistic" science that may be applied to animal victims. Knowledge of the duration of life stages of such insects as the blow-fly (the insect usually first to arrive on either a human or animal carcass) enables estimation of the time at which injury and/or death occurred.

Procedural Aspects of Forensic Examination

Perhaps the most crucial component of evaluation of a victim of an act of animal cruelty is meticulous record keeping. From the time the animals, and any evidence associated with them, are presented, veterinarians must provide a detailed record of the whereabouts of all items in their possession. This procedure is known as the "chain of custody of the evidence" or "chain of evidence." Any bodies, samples, radiographs, records, or other evidence must be carefully identified and secured in a tamper-proof manner until such time as the prosecutor deems it no longer necessary to retain them, a period that may be months or even years after the crime occurred.

The victim must be identified clearly in a manner that the veterinarian can feel confident presenting in a courtroom setting. The animal's species, breed or breed-type, sex, reproductive status, age (or estimated age), color and coat pattern, and any specific identifying features should be recorded carefully on the veterinary record. The veterinarian must be responsible for seeing that this information is accurate, whether the case involves one or multiple victims. Photographs should be taken of the animal as soon as possible after presentation for the purpose of identification; these photos are different from those taken to document the animal's condition and injuries. A card should be used in each photo that displays the date and time, and the animal's name and/or identification number

and case number. Digital and Polaroid photographs are best, because the photographer can be certain that the image is captured accurately as soon as the photograph is taken. Digital photographs should be transferred to a compact disc as soon as possible to prevent loss and tampering. Polaroid photographs degrade over time and should be scanned as digital images and stored in the same manner.

Survey radiography of the animal should be performed initially. For cats, lateral and dorsoventral views of the head, thorax, abdomen, and limbs should be taken, and the resulting films or digital files should be retained until the conclusion of the case. Additional radiographs are taken of any specific conditions identified as the examination progresses.

As the animal is examined, any sample taken from it must be retained. This can be especially difficult to remember in cases in which the victim is still alive. Hair, feces, vomitus, maggots, and other samples may be crucial evidence as the case progresses. Photographs should be taken in a consecutive manner as the examination or necropsy progresses, with the same identification information used previously (date, time, animal's name and/or identification number, and case number) visible in each photo.

Few detailed written protocols for forensic necropsy of cats are available, and providing one is beyond the scope of this text. The instructions that accompany DD Form 1626, developed by the US Department of Defense for examination of military working dogs, can be used as a template for examination of a feline victim. Additional protocols and sample forms for documentation of findings are found in a recently published text for shelter veterinarians.[22,26]

Benefits and drawbacks exist to submission of a deceased feline victim to a veterinary diagnostic laboratory rather than performance of the necropsy examination by a private practitioner assisting with the investigation of an animal cruelty case. The benefits include having (in most cases) a board-certified veterinary pathologist, whose credentials are unlikely to be challenged in court, perform the necropsy. Expanding the team of veterinary experts who are involved with a case also can strengthen the prosecution's efforts. However, a laboratory diagnostician may not be familiar with, or willing to employ, forensic techniques such as photographing each step of the process, may not be willing to testify, or may be located at some distance from the court where the case will be prosecuted, which makes it expensive for the prosecution to insist that the diagnostician be present to testify. Bodies and samples may be lost in transit or misplaced or destroyed by the diagnostic laboratory before resolution of the case. Often, the best approach is for the practitioner local to the case to perform the necropsy and submit samples for further analysis to an independent diagnostic laboratory.

Once the examination of a deceased victim is concluded, the body and any samples or evidence associated with it that have not been submitted to an outside laboratory for further examination should be identified carefully and retained. As prosecution of the case moves forward, the defense has the right to have their experts examine the evidence, and failure to be able to produce evidence can jeopardize severely or even end the prosecution's efforts.

Finally, the veterinarian should not hesitate to examine decomposed victims thoroughly. In most cases, examination of even severely decomposed animals provides useful information, and at least provides for verification of the victim's existence. Often determination of much of the animal's identifying information is possible in addition to some details of the circumstances surrounding his death, despite advanced decomposition.

SPECIFIC FORMS OF CRUELTY TO WHICH CATS ARE SUBJECTED

Thermal Injuries

Feline victims of animal cruelty are subjected to many forms of thermal injuries. These include chemical burns, fire burns (and resultant inhalation of smoke and poisonous gases), burns of hot implements ("branding iron burns"), microwave irradiation, scalding, electrical burns, heat stroke, and frostbite or freezing injuries. Cats are common victims of being set afire. Victims are sometimes bound and stuffed in mailboxes or other enclosures or may be restrained only long enough to set them on fire so that they run free. In a few such cases, charges of attempted arson and animal cruelty have been levied against the perpetrator when a burning cat has run into or under a building or other structure.

Sodium hydroxide, also known as lye, has been used for causing chemical burns to animals, The chemical is sold widely as a drain clog releaser and is used in the illegal manufacture of methamphetamine drugs. Perpetrators have been known to mix lye with flour or pancake mix to cause it to adhere more effectively to the animal's body. Battery acid also has been used, in addition to other caustic substances. Thermal and chemical burns often cause the same type of injury, and both injuries may be well hidden by an eschar, a thick scab that forms over the wound and often hides it from immediate view.

Scalding occurs when a cat is drenched with or dipped into fluid hotter than 48.8° C. The fluid may be water, cooking grease, or another fluid medium. Heatstroke, frostbite, and freezing injuries are reported rarely in cats, perhaps because victims go unseen and unreported. Such injuries occur in cats that are confined or that are debilitated or unaccustomed to the temperature to which they are subjected.

Blunt Force Injuries

Blunt force injuries include contusions, abrasions, lacerations (resulting when the impact of a blunt object is severe enough to tear the skin and underlying tissues), skeletal injuries, and internal organ damage. The implement used to accomplish a blunt force injury (a tire wrench, for example) often leaves a distinctive mark on the victim. Blunt force injuries also include binding injuries, such as occur when tape, wire, a tight collar, or other forms of binding are applied to an animal.

Impact injuries often are primarily blunt force injuries. Vehicular impact injuries include those acquired by an animal thrown from or dragged behind an automobile or other vehicle. Other impact presentations include "high-rise" and falling injuries.[27,28] Physical evidence may not be sufficient to differentiate an accidental fall from a deliberate incident in which an animal is pushed or thrown from a significant height but can be used to corroborate eyewitness accounts or a suspect's confession.

Sharp Force Injuries

Sharp force injuries include cutting and stabbing wounds, dismemberment and decapitation, skinning, and mutilation. Again,

implement analysis may be possible. In some cases, the effect of insects on a wound may mimic a sharp force injury. More than once, an animal believed to have been skinned by his attacker was actually affected by insect feeding, which created clean margins around wounds caused by another means.

Coyotes are common predators of cats, and their lifestyle often allows them to survive in a suburban community without human detection. Many cases of coyote predation on free-roaming housecats or "loosely owned" cats are wrongly thought to be the result of sharp force injuries inflicted by a person. Such events can cause hysteria within a community, and law enforcement agencies in many cases have failed to recognize the signs of coyote predation. Characteristics of coyote predation include the presence of coyotes in the area, cats injured or killed in the early morning or late evening hours, partial carcasses, crushed or torn bony and soft structures, lack of evidence of human involvement (such as binding material, knives or other instruments, tire tracks, or footprints), and a predilection for declawed cats.

Projectiles

Projectile wounds may be caused by gunshot, shotgun fire, pellets, "BBs," arrows, and blowgun darts. The mass, velocity, design, and composition of the projectile determine its destructiveness, and even low-velocity projectiles may cause serious injury and even death. This is one aspect of animal cruelty about which much has been written, and excellent guidance in evaluating such injuries is available.[29-31]

Asphyxia

Causes of asphyxia include hanging, strangulation, smothering, oxygen deprivation (by enclosure in a sealed container, for example), and administration of carbon monoxide or dioxide. Drowning is a form of asphyxia and may occur in either saltwater or freshwater, leaving distinctly different histopathological evidence. It may be necessary to determine whether a victim truly was drowned, or possibly killed by another means and then submerged so as to simulate drowning ("faux drowning").

Poisoning

Common poisons used to assault cats include ethylene glycol (the most popular, judging from anecdotal reports), rodenticides, pesticides, herbicides, prescription drugs, over-the-counter drugs (especially nonsteroidal antiinflammatory drugs [NSAIDs]), and "recreational" drugs such as marijuana and cocaine. Reports suggest that ethylene glycol is the most common substance used to poison cats intentionally (in addition to accidental poisonings that occur).

Neglect

Neglect of animals perhaps is the most common form of animal cruelty. Although many incidences of neglect are unintentional and can be addressed by education of the perpetrator, some cases are criminal and require investigation and prosecution. Presentations include starvation (both acute and chronic), dehydration, hypothermia and hyperthermia, severe parasitism, cannibalism, chronic illness, and untended wounds.

The most common and significant presentations of neglected cats are the result of animal "collecting" or hoarding, a human psychological syndrome believed to be a form of obsessive-compulsive disorder. Hoarding usually involves inanimate objects (paper, bottles, household items) but also can involve animals. Cats are easy to obtain and rather easy to confine and therefore are common victims. Animal sheltering agencies have long been familiar with the awful manifestations of animal hoarding, but the condition only recently has begun to gain attention from veterinary, human, and mental health professionals[32-35] and the media.[36] The Hoarding of Animals Research Consortium (HARC) defines an animal hoarder as someone who

- Accumulates large numbers of animals
- Fails to provide minimal standards of nutrition, sanitation, and veterinary care
- Fails to act on the deteriorating condition of the animals
- Fails to act on or recognize the negative impact of the collection on their own health and well-being and on that of other household members

Patronek has estimated that 700 to 2000 cases of animal hoarding occur annually in the United States and has characterized the animals and the people involved most commonly in hoarding cases.[33] The Hoarding of Animal Research Consortium, established in 1997 as an informal group of researchers who have an interest in hoarding, animal protection and preventing animal abuse, human-animal relations and the human-animal bond, law enforcement, psychiatry, psychology, elder abuse, social work, and epidemiology, provides a wealth of information about animal hoarding on its web site.*

Occult, Sacrificial, and Ritualistic Cruelty (and Imitation of These)

Perhaps the most sensational form of cruelty toward cats is that involving (or, more often, erroneously suspected to involve) occult, sacrificial, and ritualistic cruelty. Occult activity is that which purports to use secret knowledge or rituals connected to supernatural powers. Ritualistic acts are any acts carried out repeatedly in a systematic way. Such broad definitions encompass a wide variety of actions that range from conventional religious practices to the acts of disturbed individuals. The wide variety of occult-centered beliefs and practices defies simple classification, but most law enforcement discussions[37] recognize certain broad categories that depart from Judeo-Christian religious beliefs and practices.

Most scenarios thought to be the result of occult, sacrificial, or ritualistic cruelty are none of these. Most involve natural causes of death, such as coyote predation. The few cases that involve human activity often consist of cats that died of other causes (predation, motor vehicle trauma) that are then handled, hanged, or placed by (usually young) individuals in an attempt to simulate or emulate occult, sacrificial, or ritualistic actions or ceremonies.

In such cases, the responsibility of the investigating veterinarian is to assist with determination of whether human involvement occurred, to attempt to determine the cause of death, and to determine the sequence of death and the other

*Web site: htpp://www.tufts.edu/vet/cfa/hoarding/index.html.

events associated with the case (i.e., was the cat dead before being hung in the tree?).

CONCLUSION

The American public has demonstrated its interest in investigating and pursuing acts of cruelty toward animals, including cats. Public interest in a specific cat cruelty case will range from fanatic to nonexistent, but the veterinary community must be willing and able to respond appropriately to any case that is presented. Resources for assisting veterinarians with their involvement with an animal cruelty case are becoming more widely available and more sophisticated, and these resources should eliminate many of the obstacles that traditionally have limited veterinary involvement. Veterinarians who are shelter practitioners, because their work often requires them to assist with such cases, are perhaps the most knowledgeable about animal cruelty investigation. The Association of Shelter Veterinarians,* formed in 2003, can be an invaluable resource to private practitioners and others who wish to know more about this aspect of veterinary medicine.

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*http://www.sheltervet.org

Chapter 74

Killing Cats and Killing Birds: Philosophical Issues Pertaining to Feral Cats

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Feral cat management has become increasingly controversial in states such as Florida, California, and New Jersey. The impact of cats on wildlife populations, public health concerns, and questions about the quality of life of feral cats mean that different groups of experts, including veterinarians, often are asked to help answer management questions. One option is "trap-neuter-return" (TNR), which at its most basic includes trapping the cats, rabies vaccination, sterilization, and eartipping before the cat is returned to the original location.[1] Wildlife managers, biologists, and veterinarians, for example, tend to oppose active feral cat management approaches such as TNR in favor of lethal population control measures, whereas other veterinarians may find themselves split on the issue of TNR. The controversy has been particularly pronounced in the state of Florida, where the state department of fish and wildlife ruled in 2003 that it would no longer support and/or tolerate the practice of TNR and the existence of managed cat colonies.[2-4] A 500-cat colony in Key Largo became the focus of national attention as the state agency and several environmental organizations claimed the cats were contributing to the decline of two endangered species in Key Largo: the Key Largo woodrat (*Neotoma floridana smalli*) and the Key Largo cotton mouse (*Peromyscus gossypinus allapaticola*).[5]

Professionals in fields related to wildlife conservation are asked to contribute technical expertise to a controversial subject, and sometimes the advice of one group of experts conflicts with that given by the others. This technical information is difficult enough to locate, evaluate critically, and put into practice. The most difficult questions related to feral cat management, however, may be the philosophical problems rather than the technical ones. Although researchers may debate the efficacy of various forms of birth control (e.g., surgical sterilization or immunocontraception), the ethical question of what *ought* to be done is a far more perplexing issue. Some of these complex philosophical issues are the topic of this chapter.

In part, this complexity results from the fact that we are not even sure what feral cats are. Are they just unsocialized individuals within the broader class of domestic cats, or does a real difference exist between *feral* and *stray* or *barn* cats? Often commentators simply adopt a convenient definition before focusing on technical questions about birth control. Patronek[6] adopts the language of "free-roaming and feral cats" and provisionally that is the practice I follow here unless otherwise stated. But this still leaves the conceptual, philosophical problem unanswered, what is a *feral* cat?

Even with an assumed agreement regarding the definition of "feral" cats, related questions arise regarding the effect of these cats on their environments. Epistemological questions abound: what do we know about the ecology of feral cats, and what do we not know? Much is unknown, for example, about the putative *negative* effect that cat predation has on wildlife populations. From the known *fact* of predation, people sometimes jump to the *conclusion* that such predation is automatically harmful to the prey species population. But is this conclusion supported by quality evidence? And how does this conclusion affect the management questions of what ought to be done with feral cats?

Answers to these questions often depend on aesthetic concerns and involve a possibly contradictory aesthetic appreciation for the cat and aesthetic concern for "the environment." The Greek root of the term *aesthetics* is "perceive." Some people perceive the cat to be an alien, exotic species with no appropriate place in the environment. Others perceive the quality of wildness that the cat represents and for that reason believe the cat has a rightful place in natural systems.

Arising out of all these philosophical questions usually is the ethical response, most often posed as a binary decision between killing the cats or saving the cats. Too often, the complexity of real-life management considerations gets lost in this false dualism. But feral cat management should not be left to a simple coin toss between the competing aesthetic perceptions of cat lovers versus cat haters. A careful examination of the conceptual assumptions and implicit value biases of either side is a necessary first step to achieve better policy.

DEFINITION OF FERAL CATS

Ontology is the philosophical study of reality. Ontological questions about feral cats can include, for example, the question of what is "feral" or "wild"? Is ferality a real property of cats and of other feral animals, or is this simply a concept assigned by human beings to part of nature with practical and heuristic benefits? In other words, do the terms correspond to "real" or natural categories in nature or are such terms inescapably relational and dependent on human perception for definition?

Related taxonomic questions may include the following. How does the domestic cat compare genetically to the African wildcat? What is the essential nature of the domestic cat as compared with the wildcat? These topics relate more broadly to the philosophical question of *natural kinds* and biological essentialism.[8-12] Is the cat species a natural kind within nature? Is ferality an essential property of domestic free-roaming cats within the category of species?

Considerable philosophical ambiguity surrounds the concept of "feral." In one of the few published studies on feral animals in the United States, McKnight[13] listed nine conceptual issues that affect the definition of "feral":

1. Does the animal population need to be "established" in the wild to be classified as feral?
2. Do animals living in close proximity to human beings count as feral?
3. Does being unowned mean a cat is feral?
4. Must a stable population be reproducing in the wild to be considered feral?
5. Are there *degrees* of ferality?
6. Do differences exist between the terms feral, unclaimed, stray, and loose?
7. Can an animal be feral part of the time?
8. Are feral offspring themselves "feral" or "wild"?
9. Can a spayed, neutered, gelded animal be considered feral?

McKnight acknowledges that zoologists and taxonomists do not agree on these issues, and he adopts this definition: "Ferality here is considered in a broad sense; that is, a feral animal is one that was once domesticated, or with domesticated ancestors, but is now living as a wild creature. It is not under the effective ownership of humans, and does not receive protection, care, or food as a deliberate gift from [humans]."[3,13] By McKnight's definition, many so-called feral cats, especially in managed colonies, would not be considered feral cats. Such conceptual ambiguities about the cat's ontological status lead to real political problems for cat management, including conflicting interpretations of such categories as domestic verus wild, owned versus unowned, and managed versus feral.

Animal behavior itself also complicates the task of definition. For example, a breeding population left alone can and often does revert to a wild state under conditions of natural selection rather quickly. Indeed, Mayer and Brisbane list 20 different historically recognized subspecies of wild pig that have received specific and subspecific taxonomic designations.[14] Conceivably, if left alone, a feral cat population could re-evolve into a new form more closely resembling the cat's wild ancestral lineage, and this new variety could in turn become a highly valued addition to the fauna of a given region.

In practice, most veterinarians and shelter workers who deal with cats on a regular basis tend to adopt a behavioral concept of "feral" cats: ferals are those cats that are too unsocialized to approach, handle, or treat medically without taking extraordinary measures.

EXISTING KNOWLEDGE REGARDING FERAL CATS

The Example of Predation Effects on Wildlife

One of the major sources of controversy in feral cat management concerns their suspected impact on populations of birds, rodents, rabbits, and other small animals. Despite many studies, the ecological effects of cat predation are exceedingly difficult to gauge. In a few documented cases of cat predation on island species, the correlation and results have been demonstrated clearly. A single cat was responsible for the extinction of a flightless wren in New Zealand, the Stephens Island Wren (*Xenicus [Traversia] lyalli*).[15]

In contrast, the effect of cats on prey populations in mainland settings is uncertain. One problem with predation studies is the common failure to distinguish between what ecologists call "additive" or "compensatory" predation. Does cat predation *add* to a base level amount of predation and thereby increase the overall mortality of a prey population in a local area? Or does the predation replace other forms of mortality and merely compensate for mortality that would occur anyway? Few cat predation studies allude to this problem, and virtually none address it directly in the data analysis. Furthermore, studies rarely attempt to establish the abundance of prey; therefore no data exist whether cats intentionally *select* certain types of prey or prey on whatever is available. Much of the literature cites one or two studies; few people take the time to examine the cat predation literature in total. However, some wider appreciation of the methodological difficulties and constraints is important in consideration of both sides of this debate.

For example, many environmental organizations cite one or two well-known studies of cat predation, and such organizations often exaggerate the findings of these studies. Frequently cited are the study in England done by Churcher and Lawton[16] and the estimates of cat predation on wildlife in Wisconsin developed by Coleman, Temple, and Craven.[17] Neither study, however, is a reliable guide to judgment of feline impacts on wildlife elsewhere.

Therefore, other than in a few clearly documented cases of cat predation on island species of prey,[18-20] the impact of cats on prey populations is hard to assess. Occasionally even the impact of cat predation in island settings is blown out of proportion by extrapolation; that is, by the assumption that what happens in one location must cover all island locations. However, cat predation on islands is not always ecologically damaging. For example, Apps studied stomach contents and prey caught on Dassen Island, South Africa, and reported that rabbits and birds "contributed equally to the cats' diet." This statement may lead to the conclusion that the effect on birds was significant. But Apps also reports that most of the birds were scavenged, and therefore "the impact of cat predation on the bird populations was insignificant."[21] Tidemann, Russack, and Yorkson speculate that cat predation has a net positive ecological impact because of the predation on rats.[22]

Too often, studies are cited without being fully or critically understood. For example, in one of the most widely cited

studies, Churcher and Lawton collected data on what cats brought home to an English village over a period of a year, and their study yielded one of the highest estimates of predation on birds in the predation literature. Nearly 30 per cent of the diet of cats was estimated to be birds.[16] And yet the bird species that dominated the cats' diet was the English house sparrow, whose garrulous colonial habits and large numbers led the authors to speculate that the birds' behavior was likely a significant causal factor contributing to cat success at predation. In this way, later studies that extrapolate from Churcher and Lawton unwittingly use a biased number that may apply only to house sparrows and not to other forms of avian prey that cats may encounter.

Other types of bias can creep into such predation studies in well-known ways. Scat analyses may highlight the dietary habits of animals selectively whose scats are easiest to find, such as those closest to human habitation. Stomach analyses gauge only what a dead cat had to eat as its last meal. Historically, the number one source of dead cats for such analyses has been road-killed cats, who may be preying upon roadside species of prey more than a normally distributed population of cats scattered across the entire landscape.

Another source of bias can arise in studies that inventory the amounts of cat prey brought home. Rabbits probably are most difficult to carry and perhaps are eaten on the spot more frequently than smaller items.[23] However, many researchers have assumed, as do Churcher and Lawton, that whatever is inventoried at home is a representative sample even if only half the total prey is delivered to the doorstep.

Cat behavior while hunting also must be taken into account in the effort to form an overall picture of the effects of predation on wildlife. In evolutionary and bioenergetics terms, it is more efficient (and easier) for a cat to sit quietly along a grassy runway in a meadow waiting for a vole or mouse to come along than it is for the same cat to attempt to catch a bird that can fly away.[24] Evolution favors efficiency. Young cats attempting to catch birds eventually may tire of the game and concentrate primarily on the easier game of small mammals. Rabbits of course are the easiest game, especially when plentiful, because they are often out in the open, the young are easy to catch, and they represent more of a meal when compared with a mouse or bird weighing less than an ounce. Given these likely contributing factors, in areas where rabbits are common, estimates of 30 per cent birds in the cat's prey diet seem highly unlikely.

The Wisconsin Study as an Example of the Problem of Mutant Statistics

One widely cited and misrepresented study that estimates a high percentage of birds in cat diets is the "Wisconsin study" conducted by Coleman, Temple, and Craven,[17] who are cited for having demonstrated that tens of millions of birds are killed by cats in Wisconsin per year. "Recent research[10] suggests that rural free-ranging cats in Wisconsin may be killing between 8 and 217 million birds each year." Citing their own "study," they write, "The most reasonable estimates indicate that 39 million birds are killed in the state each year."[25]

Coleman and Temple arrive at their estimates by multiplying (1) the estimated number of cats in Wisconsin, (2) the total number of prey items caught per cat per year, and (3) the percentage of those prey items that are birds. To arrive at their highest estimate, they calculate that 2 million cats each catch one prey item per day, and they estimate that 30 per cent of those prey items are birds.

What criteria do Coleman and Temple use to judge what is "most reasonable"? This is unclear. They simply take their middle estimate from a completely unrealistic range; because if in fact their estimate should be closer to "between 3 and 40 million birds each year" are killed by cats (as I believe it should be, using their own method of estimation), then their own method of arriving at their "most reasonable" figure would result in a far lower number—approximately 8 or 10 million birds a year:

(a) 1.4 million cats × 14 prey/yr × 5 per cent prey birds = 980,000 birds per year
(b) 1.7 million cats × 50 prey/yr × 10 per cent prey birds = 8.5 million birds per year
(c) 2 million cats × 100 prey/yr × 20 per cent prey birds = 40 million birds per year

More troubling, however, is what happens to Coleman and Temple's method of defining the "most reasonable" estimate when their work is cited in United States Fish and Wildlife Service (USFWS) funded publications. The *Migratory Songbird Conservation* pamphlet[26] reports the Coleman and Temple estimate as being 20 to 150 million birds preyed upon each year by cats, as if to suggest that the USFWS is skeptical of Coleman's and Temple's numbers. However, if I am correct, and the most likely or *actual* "most reasonable" figure is 8.5 million birds per year (using Coleman's and Temple's method), then the reality actually would be *far* below what the USFWS reports as the official Wisconsin estimate. This statistic (20 to 150 million birds per year killed by cats in Wisconsin), cited by the federal government, is now in a widely distributed brochure and is available on the Internet.

Many people assume the information is accurate and that the USFWS is reporting the Wisconsin study accurately. The fact that the brochure narrows the range is one indication of how problematic the Coleman-Temple figures are: as if to acknowledge that a range of 8 to 217 is improbable, the authors of the USFWS brochure narrow the gap to a range with which they apparently feel more comfortable. And yet if the real loss of birds in Wisconsin to cat predation is 8 to 10 million birds, then this publication overstates the actual extent of the problem dramatically.

Coleman and Temple defend their figure of birds being 20 per cent of the prey items of cats, citing a work by Fitzgerald[27] who has studied cat predation extensively in New Zealand. And yet Fitzgerald himself gives no indication of how he arrives at the 20 per cent average: how he reconciles studies done by weight, by frequency of occurrence, by volume, and by countless other methods used to estimate cat predation. For example, suppose Fitzgerald includes the New Zealand study that reports birds "consisting mainly of introduced species, including turkeys, were both frequent . . . and important by weight"[28] in the diets of predatory free-roaming cats. And yet if the bird content by weight primarily is farm-raised and free-roaming domestic turkeys, how does this study have any bearing on Coleman and Temple's estimates of cat predation on migratory songbirds in the United States? Curiously, Langham analyzed 361 cat scats and determined that 7 per cent of the scats by weight consisted of sheep remains. Does this signify that cats are a major threat to sheep? To be serious, without some indication of the conditions under which the birds

are taken, the figures given for predation on birds are meaningless.

The Wisconsin figure of 8 to 217 million has become an example of what Best refers to as a "mutant statistic"[29] whose origins and genesis have been generally lost to the people who cite it. Coleman, Temple, and Craven published this "best guess" originally in a popular nature magazine[25] but then later self-cited the same report as "research."[17] This typically goes unnoticed, and subsequent authors too often have tended to cite the 8 to 217 million figure uncritically as "research." For example, in 2003, wildlife biologists charged with writing a Florida report on cat impacts in that state argued that their statistics are conservative in comparison with the Wisconsin study but write, "We believe these estimates are conservative and, if the highest predation rates from Wisconsin are more accurate, cats might well kill many millions more mammals and birds in Florida."[4,7] The heavy reliance on this type of speculative evidence offered by experts in the wildlife field is irresponsible.

The Wisconsin "research" figures have taken on a life of their own in the so-called "gray literature," which Auger defines as "information produced on all levels of government, academics, business and industry in electronic and print formats not controlled by commercial publishing."[30] Even biologists who may have good reason to suspect that the Wisconsin statistics do not reflect reality still manage to cite the Wisconsin numbers as a sort of "worst case scenario."[4,7]

However, for all of the many references made to the Wisconsin study, few researchers have really evaluated the weight of the evidence supporting their 8 to 217 million bird deaths estimate. For example, Coleman and Temple "estimate that 23 percent of [cats'] diet consists of birds," a figure that "is consistent with other studies indicating roughly 20-30 percent of free-ranging cat kills are birds."[25] This statement is grammatically correct in the limited sense that their choice of percentage is consistent with such studies, but the authors neglect to mention that their selection of these studies does not reflect the norm for cat predation studies *overall*. As many, if not more, studies exist that indicate cats kill few or no birds.

A survey of studies reveals that, depending on the location, the percentage of prey that are birds in a cat's diet varies roughly from 3 to 5 per cent to 20 per cent, with 10 per cent being as good a rule of thumb as any.* Pearson[55] conducted a 1-year scat analysis in California; 4771 remains were of rodents, 21 of rabbits, and 8 were birds. Tidemann, Russack, and Yorkson[22] speculated that cats have a net positive impact on bird populations on Christmas Island in the Indian Ocean because of their predation on rats. Studies reporting "trace" on the one end, and those reporting percentages up to 30 per cent, safely can be considered anomalies, at least for the purpose of generalizing or extrapolating to a broader, continental context. In other words, a far more globally plausible estimate is that 10 per cent of the prey of *all* cats are birds. It is not a globally plausible estimate to say that 30 per cent of the prey items taken by cats are birds.

Furthermore, Coleman and Temple mislead their readers potentially in their sidebar titled "How many birds do cats kill?" by highlighting one data point: "One rural cat was recorded to have killed 1,690 animals in an 18 month period."[25] The likely effect is that many readers may generalize this statistic to all cats. What Coleman and Temple neglect to say is that the cat in question belonged to Michigan biologist G.W. Bradt, who recorded the species composition of the 1690 deceased animals meticulously.[33] Of that number, Coleman and Temple neglect to inform their readers that only 62 of those prey items were birds and 54 of those were English house sparrows. The other eight birds included one flicker, one meadowlark, one robin, two goldfinches, two chipping sparrows, and one white-throated sparrow.[33] These totals are mentioned here in specific detail because they illustrate the low incidence of bird kill in the diet of even an accomplished feline predator, and this is reported by a thorough and ably qualified field naturalist: eight non–English house sparrow birds over 18 months out of 1690 prey items.

Based on this and other extrapolative evidence, however, what is Coleman and Temple's conclusion about cat predation on birds? "Clearly, free-ranging cats are a major predator of birds in rural Wisconsin."[25]

Other reports that have depended on stomach or scat analyses of relatively small numbers of cats may be biased if a small number of cats have a large number of bird kills, a skewed distribution that would tend to drive the mean upwards. Or, in some studies, cats in farm settings were adept at killing young farm ducks and pheasants; stomach analyses listing bird content by volume would be similarly skewed. In Sweden, Liberg[47] studied 1437 scats and broke down the results by "house cats" and "field cats." Field cats consumed 294 g/day and house cats 66 g/day. Birds made up 3 per cent (by weight) of the prey of house cats, half of which was pheasant. Field cats had fewer instances of birds in scats, ranging from 0 to 3 per cent by weight in the field scats.

The author of a study of cat predation on ringed (banded) birds in England notes that, although swallows are the least susceptible birds in the list of bird species preyed upon by cats, he has personally witnessed cats jumping off shed roofs to catch swallows. "A few cats are successful at catching flying swallows by pouncing from a shed roof and catching the birds in flight," reports C. J. Mead of the British Trust for Ornithology, adding "I have even seen swifts *Apus apus* taken like this."[59] The anecdotal use of a few cats to generalize about all cats' effectiveness at catching swifts clearly would be unwarranted, yet this is what much of the cat predation literature appears to do regularly.

To my knowledge no researcher has yet done a comprehensive analysis of all the predation studies from all continents and reconciled them to account for differences in method and approach. If someone were to undertake such analysis, it would still produce only a raw average of what is happening in numerous, diverse contexts, and this single raw number would be used to represent a range of phenomena that may never be understood adequately.

Perhaps the most honest statement in all the cat predation literature is made by Martin, Twigg, and Robinson[49] who studied the stomach contents of 93 cats in Australia. "We accept that it is not possible to make any inferences concerning the real impact of feral cats on prey populations from dietary studies."[49] I believe that this statement generally is true. This is not to suggest that no basis for concern exists regarding cat impacts on wildlife in specific contexts. In Florida, government attempts to reintroduce radio-collared marsh rabbits were largely thwarted by cats: 27 of 43 radio-collared rabbits died over 2.5 years, and 53 per cent of that mortality resulted from

*References 6,18,20,21,23,27,28,31-58.

predation by domestic cats.[60] In this particular case, however, the question still needs to be asked: either the government should rethink its decision to reintroduce the rabbits, or else the state should remove the local cat population before implementation of the reintroduction program. In any event, knowledge of a specific area and of a specific problem is more likely to lead to a political outcome in which both sides can agree than with a blanket injunction against all cats in general.

Once researchers begin to produce accurate information on cat predation impacts, we will be able to make more informed management decisions, including decisions to protect endangered and other at-risk species. However, assuming that in many areas no demonstrated negative impact exists on such species, we are still left to consider whether feral cats "belong" in various settings. This question then boils down to the essentially competing aesthetic preferences between cat advocates and anti-cat activists, who argue that because the domestic cat is a nonnative species, the wild has no place for ferals.

CATS AS EXOTICS AND THE PROBLEM OF NATIVISM

Aesthetic concerns mostly are unacknowledged in debates about "exotic" versus "native" species. Why do we care about native species more than exotics? What kind of nature do we want, one with cats or without cats? Perhaps the most strongly held view on the part of wildlife advocates is the normative judgment that the cat as a nonnative predator is of less value than an individual of a native species. This judgment often is simply *assumed* rather than argued; but the argument rests on a distinction between what is natural (wild vs. native) and what is artificial (domesticated vs. exotic), which again, is not a technical or a scientific distinction as much as a philosophical one.

As John Rodman observes, from an ecological restoration perspective, substantive and functional questions exist that relate to the ecology of nonnative or exotic species. Strict ecological restoration more clearly would preclude the introduction of an exotic species into a habitat. In other cases, exotics might be "good" if they serve a uniquely valuable service functionally. Iceplants (*Carpobrotus* spp.) can aid rapid dune stabilization in coastal zones, for example.

Moreover, some philosophers have argued that the preference for native species simply is bigotry. Peretti argues that the nativist bias in conservation biology "is scientifically questionable and may have roots in xenophobic and racist attitudes."[61] Although this may be a bit extremist in relation to feral cats, it does suggest that the *assumption* that nonnative animals are bad requires constant examination.

The *fact* that cats are an "exotic," nonnaturally evolved predator in the North American ecosystem does not *entail* the moral conclusion that cats *ought* to be eliminated. This conclusion is not warranted by the mere fact of the cat's ontological status. An additional moral premise or set of moral premises must bridge the gap from factual premise to moral conclusion. In other words, the exotic issue raises the philosophical problem known as the "is-ought" problem: from a descriptive statement of what *is*, it is logically invalid to conclude automatically from that fact to what *ought* to be the case without some type of intervening moral argument.

The philosopher David Hume was the first to draw attention to this problem in his *Treatise of Human Nature:*

> In every system of morality, which I have hitherto met with, I have always remarked, that the author proceeds for some time in the ordinary way of reasoning, and establishes the being of a God, or makes observations concerning human affairs; when of a sudden I am surprised to find, that instead of the usual copulations of propositions, is and is not, I meet with no proposition that is not connected with an ought, or an ought not. This change is imperceptible; but is, however, of the last consequence. For as this ought, or ought not, expresses some new relation or affirmation, 'tis necessary that it should be observed and explained; and at the same time that a reason should be given, for what seems altogether inconceivable, how this new relation can be a deduction from others, which are entirely different from it.[62,63]

Hume argues that it is never deductively valid to reason from factual premises to moral conclusions. Many philosophers consider it a fallacy to reason in this way: the logical problem of the "is-ought fallacy" also is referred to as "Hume's problem" or as the "naturalistic fallacy" (i.e., the fallacy of arguing that what is natural is good).

One sees the fallacy committed in countless documents pertaining to feral cat management. The claim that the cat's exotic status should count against it often is employed in policy arguments about cats as a conversation-stopper, that the cat is an exotic "alien" is supposed to trump all other values in the debate. For example, the *Migratory Songbird Conservation* pamphlet published by the US Fish and Wildlife Service states: "Feline predation is **not** 'natural.' Cats were domesticated by the ancient Egyptians and taken throughout the world by the Romans. Cats were brought to North America in the 1800s to control rats. The 'tabby' that sits curled up on your couch is not a *natural predator* and has never been in the natural food chain in the western hemisphere."[26]

The claim that feline predation is not natural carries with it implicitly the normative judgment that feline predation is wrong, or at least that allowing feline predation is wrong.

Similarly, Carol Fiore writes:

> Remember two important points: firstly, it is against the law to injure birds, and secondly, don't shrug your shoulders and say ". . . but that's what cats do. It's a normal part of life." Cats are *introduced* predators. They are *not* a natural part of the ecosystem of North America and our native wildlife did not evolve in the face of this accomplished predator. When *native* wildlife preys on birds, that *is* part of the "circle of life." Cats do not face the population controls that other species do and their current numbers are staggering and continuing to grow.[64]

These are tricky arguments for bird advocates to make. The statement, "They are not a natural part of the ecosystem of North America and our native wildlife did not evolve in the face of this accomplished predator" could apply as well to such species as the North American lynxes *(Lynx canadensis)* and bobcat *(Lynx rufus)*, both of which are migratory latecomers to North America, a fact noted by Leyhausen.[46] Admittedly, the lynx migration to North America does not have an anthropogenic cause; on the other hand, apparently "our native wildlife did not evolve in the face of [these] accomplished predator[s]" either. Fiore cannot have it both ways: either she must come up with additional moral premises to supplement her anti-cat argument or the argument itself is invalid.

Once we realize that we need more than blanket assertions about "exotics," we are left with going to a case-by-case analy-

sis: in the case of cat predation on endangered species, it is the *harm* to the species itself, and not the cat's exotic status per se, that provides the morally relevant justificatory rationale for drastic measures up to and including the removal and killing of the cats.

That the predation pressure is "unnatural" is not a good argument either, for it may be the case that such predation is exerting a selection pressure on the prey species and altering its phenotype (for better or worse). Something like this predator-induced phenotypic plasticity appears to be at work with larval newts[65] and also may occur with cat predation. Again, why bemoan the fact that cats prey on certain individuals within a species if the prey species *on the whole* can adapt to that pressure? We may be watching evolution in process, which in some contexts may even be celebrated.

Furthermore, no statistically valid single number holds in all cases that represents the percentage of prey of a specific species killed (birds or whatever else is of interest). Perhaps, in island settings, the percentage of prey that are birds is very high; in woodland settings, very low; and in other cases, somewhere in between. The efforts by Coleman, Temple, and others to pin a single number on predation on birds is logically doomed to fail; and in fact, most applications of Coleman's and Temple's numbers have tended to come up in discussions of woodland or pastoral, non-island settings.

In Florida, the Florida Keys would appear to be an apparent exception to this claim that biologists overextrapolate such numbers to inappropriate nonisland settings. But in NSF-sponsored field work in 2003 "on the ground," I revealed that a much-criticized colony of 500 cats at the Ocean Reef Club of Key Largo is approximately 2 miles away from the nearest habitat of endangered species, with a flooded red mangrove swamp to cross in between! Moreover, Humphrey reports that in several years of trapping on federal land in Key Largo, not once did he catch a cat in his traps.[66] Thus the claims by the American Bird Conservancy that the Ocean Reef Club cat colony is contributing to the loss of the Key Largo woodrat and to the Key Largo cotton mouse appear to be unfounded.[67]

Managers in places such as Florida also are left with the apparent paradox of advocating the extinction of one exotic species (cats), while maintaining healthy populations of exotic species that potentially are far more harmful, such as the feral pig. The difference, of course, is that the feral pig is a game species that is hunted and that provides satisfaction to hunters and generates revenues for Florida's wildlife management programs. The cat provides no such economic benefit to Florida's fish and game commission, but it does provide satisfaction to cat lovers.

Philosopher Mark Sagoff observes that government agencies eventually could commit to spending billions of dollars to control alien species just as public agencies in the past have spent billions to control forest fires. Fire suppression policy seems misguided, and in fact the federal government today is adjusting its fire policies to work on more of a case-by-case basis. Similarly, writes Sagoff, "The movement of species has been a constant occurrence in natural history—like the occurrence of fire. Before we commit a lot of (taxpayer) money to controlling exotic species, it might be helpful to understand why we should treat alien creatures any differently than we treat native species."[68] Managers need to remember that they are dealing with more than just another wild animal (e.g., a wild pig) but rather with an animal that in its domestic state is the highly valued pet cat in many homes across the country.

"Those who call for additional resources to fight exotic species," adds Sagoff, "typically defend their position by pointing to examples of non-native species, such as the zebra mussel, that have had costly or disruptive effects. *Examples, however, are not arguments*" (emphasis added).[68] This is the key message that veterinarians, cat activists, and wildlife managers need to keep in mind. For every unambiguous example of a Stephens Island wren made extinct by cat predation, thousands of bird species survive in the presence of such predation. Isolated examples of indirect negative impacts[41] also are not good arguments for the wholesale elimination of cats in the wild.

Feral cat management also must acknowledge the practical side of managed cat colonies as a tool of population control. Official organizations that oppose cat-neutering programs often do not have a viable, economically self-sustaining program proposal as an alternative. Opponents of cat-neutering programs insist that euthanasia or fenced cat sanctuaries are the only appropriate means of dealing with cat overpopulation,[69,70] and yet these programs have failed to attract much volunteer support or funding to date. Few veterinarians would offer to do hundreds of cat euthanasias, for example, in one afternoon, whereas many volunteers give their time to participate in trap, neuter, and release clinics.

CONCLUSION

Are domestic species/animals more morally worthy than wildlife? Philosophers have long recognized that moral worth is partly determined by *relation*. Human children are valued more highly and worth more to their own parents than are the children starving halfway around the globe. Our moral obligations are clearer to close relations than to those who are further away from us. Again, the wild feral cat is not just another feral animal but the close relative of the animal asleep on people's sofas.

The fact that some people *appreciate* cats matters morally and ethically. The same is true of people who *appreciate* wildlife. The relation to domestic animals is somewhat more direct than that toward wildlife. Human relation to a wildlife species always is more *abstract* than personal or direct, as implied in "relation to species." How does one have a relation to a "species"?

Environmentalists who assume automatically that cats are everywhere throughout the landscape could look to Henry D. Thoreau, a naturalist, and who writes in *Walden*, "once I was surprised to see a cat walking along the stony shore of the pond, for they rarely wander so far from home."[71] This was a significantly rare enough event for Thoreau to lead him to record the incident in his journals. Similarly, Aldo Leopold, considered by many to be the father of modern wildlife management, once surveyed more than 300 "woodsmen" for evidence of cats' breeding in the wild, and came up with but a handful of accounts.[72] Wildlife managers have to confront the anecdotal evidence that has been offered historically, which suggests that domestic cats do not wander far from home and that they do not breed in great numbers in wild areas away from human settlement.

Similarly, wildlife managers, veterinarians, and biologists who place a lot of weight on the exotic versus native distinction may consider another value angle: the wildness inherent in

the act of predation itself. The killing that cats do is as much a part of nature as is any given assemblage of individual animals that human beings group together in the classification of "species." Why not value the *wildness* embodied by the feral domestic cat if one's concern is *wild*life?

Desmond Morris recalls that as a boy in Wiltshire he spent "many hours lying in the grass, observing the farm cats as they expertly stalked their prey," which led subsequently to a lifelong involvement with animals and responsibility for big cats as curator of mammals for the London Zoo.[73] The act of predation is for Morris, something to be studied, enjoyed, celebrated even.

Again, Henry D. Thoreau also seems to have recognized something of this value when he wrote in *Walden:* "The most domestic cat, which has lain on a rug all her days, appears quite at home in the woods, and, by her sly and stealthy behavior, proves herself more native there than the regular inhabitants."[71] Thoreau's appreciation for the wildness of the cat's sly and stealthy behavior may form the basis of a new environmental aesthetic,[74,75] one in which the wild aspects of the feral cat's predatory existence could be appreciated rather than eliminated.

These ideas and moral arguments also are crucial for veterinarians to appreciate. An understanding of the underlying assumptions is imperative to become an informed participant in the great cat debate.

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Chapter 75

Zoonotic and Vector-Borne Infections in High-Density Cat Populations

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For those interested in zoonoses, multiple-cat households and populations (described in shorthand as "catteries" throughout this chapter) may be fascinating natural laboratories of disease and offer the potential for observation of rare or unusual diseases and, more practically, opportunities for population management strategy assessment.[1] Numerous relatively high-density cat populations exist, including breeder catteries, pet stores, shelters and rescue facilities, and feral cat colonies. Many infectious diseases (and arthropod parasites) occur at higher prevalence in high densities of host populations. This problem is exacerbated in shelters, feral cat populations, and some other catteries by population risk factors for zoonotic infections, such as high turnover, stress or debilitation, malnutrition, and prior inadequate care. A significant number of zoonotic and vector-borne diseases threaten cats and their human caregivers, many of which occur, among domestic animals, only or primarily in cats. Thus cat populations also may serve as sentinels for agents of possible biological warfare such as the agents of plague, tularemia, and pox. This chapter emphasizes population presentations of some feline zoonotic, vector-borne diseases, including the most typical presentations, risks, and management strategies. These feline zoonotic vector-borne diseases are summarized in Table 75-1. The last column refers to agents that are regulated by the U.S. Centers for Disease Control because of their potential for use in bioterrorism.

In any multiple-cat facility, a medical team or medically oriented husbandry team (sometimes consisting of a breeder and his or her veterinarian) can and should assess the population health periodically by a walk-through of the facility (if one exists), performance of physical examinations in some or all of the animals, and evaluation of written records such as records of productive pregnancies in breeder catteries or diagnostic test results in pet stores.[2] The walk-through should occur daily and be accompanied by a written summary. The physical examination should occur more often in high-risk populations (possibly daily or weekly in shelters and pet stores) and less frequently in stable populations such as many breeder catteries (unless problems have been noted).

Based on these observations, medical problems can be divided by system: dermatological, respiratory, gastrointestinal, systemic (including weight loss, low energy, and other nonspecific findings), neurological, reduced fecundity (pregnancy success and kitten survival), or other (e.g., ocular). In addition, zoonotic diseases should be considered that typically do not result in clinical signs in cats but that still may be infectious to human beings. This chapter addresses four systems: dermatological, respiratory, genitourinary, and systemic. These were chosen because the zoonotic problems associated with them either are common or are of major clinical importance either to cats or human beings and, even if rare, require vigilant surveillance.

DERMATOLOGICAL SIGNS

One of the most commonly affected systems in multiply housed cats is the integument, and multiple cats in a group typically are affected to varying degrees simultaneously. Although it is outside the scope of this chapter to give a complete rule-out list for dermatological diseases in cats, a population-wide, likely infectious problem can be strongly suspected if the problem occurs in multiple cats at the same time, appears acutely in the cat population, or appears moderate to severe in two or more cats. Important considerations if multiple cats are affected include arthropod infestations (fleas, mites, ear mites, ticks, chiggers, and lice), in addition to fungal dermatopathy (see Chapter 32 for a detailed discussion of dermatophytosis). Because of their zoonotic implications, only fleas and ticks are discussed here.

Fleas

Ctenocephalides felis fleas are wingless insects that feed on the blood of their hosts as adults. This flea species is not host-

Table 75-1 | **Zoonotic Disease Agents of Cats**

AGENT	VECTOR	MAIN ROUTE OF TRANSMISSION	CAT DISEASE	HUMAN DISEASE	SELECT AGENT
Rickettsia felis	Cat flea *(C. felis)*	Flea bite	NA	Murine-like typhus	Yes
Rickettsia typhi	Rat flea *(X. cheopis)*	Flea bite	NA	Murine-typhus	Yes
Rickettsia akari	Mouse mite *(L. sanguineus)*	Mite bite	NA	Rickettsialpox	Yes
Rickettsia rickettsii	Ticks: *D. variabilis* (eastern and western US), *D. andersoni* (western US)	Tick bite	NA	Rocky Mountain spotted fever	Yes
Coxiella burnetii	Multiple tick species	Aerosolization or ingestion	Asymptomatic or mild febrile illness	Q fever, endocarditis	Yes
Bartonella henselae	Cat flea *(C. felis)*	Inoculation of flea feces via bite or scratch	Asymptomatic or mild febrile illness	Cat scratch disease, endocarditis, bacillary angiomatosis	No
Bartonella clarridgeiae	Cat flea *(C. felis)*	Inoculation of flea feces via bite or scratch	Asymptomatic or mild febrile illness	Cat scratch disease	No
Bartonella quintana	Human body louse *(P. humanus humanus)*	Inoculation of infected louse feces	NA	Trench fever, endocarditis, bacillary angiomatosis	Yes
Ehrlichia canis	*R. sanguineus*	Tick bite	Asymptomatic to febrile illness	Monocytic ehrlichiosis	Yes
Anaplasma phagocytophilum	*I. pacificus* and *I. scapularis*	Tick bite	Asymptomatic to febrile illness	Granulocytic ehrlichiosis	Yes
Francisella tularensis	Ticks *Dermacentor* spp, *Amblyomma americanum*	Exposure to infected prey animals	Asymptomatic to fever, skin ulceration, and lymphadenopathy	Tularemia	Yes
Yersinia pestis	Fleas	Fleas, exposure to infected cat	Pneumonic plague	Bubonic and pneumonic plague	Yes
Borrelia burgdorferi	*I. pacificus* and *I. scapularis*	Tick bite	Mild fever and joint stiffness	Lyme disease	Yes

NA, Not applicable.

specific and can be found on dogs, opossums, and people, in addition to cats. Larval fleas feed on material defecated by adult fleas (which is high in host blood content). The pupal fleas protect themselves in environmentally resistant cocoons, from which they metamorphose into adults. Eggs are laid directly on the host. Although individuals in all three stages may remain on the host, numerous others survive in the environment for several months without feeding (depending on the temperature and humidity). Therefore flea infestation can persist in a cattery as an animal and environment problem, particularly in areas with increased ambient temperature and humidity.[3]

Allergy to flea saliva is one of the most common causes of alopecia and dermal inflammation in cats. Only a few flea bites are required to trigger inflammation and pruritus in severely allergic cats, but other less allergic cats may harbor large flea loads with few clinical signs. Typical clinical presentations include erythema and alopecia, usually on the ventral abdomen and at the tail head. Fleas and flea dirt (high blood content flea feces) may or may not be apparent. In addition to the direct dermatological effects of fleas in cats, flea infestation in a cattery is a serious concern because of the possibility of spread of flea-borne pathogens, including tapeworms, *Bartonella* spp. (see Chapter 4), and *Rickettsia felis*.

With the advent of topically applied systemic anti-flea therapy, effective control of fleas in individual cats has become much easier. Severely affected cats (particularly with extreme inflammation or secondary bacterial infection) should receive medicated baths to treat adjunctive problems. Young kittens should be treated aggressively to remove fleas, which can cause severe anemia, while insecticides safe for kittens are used. Flea infestation management in the environment also is important to prevent infestation in newcomers, human beings, and any cats not up-to-date on systemic therapy. Considerations for environmental management include insecticides, silica, borate, and insect growth regulator. Several papers address on-cat and environmental management of fleas.[4,5]

Ticks

Ticks infest cats occasionally; after biting, they cement themselves into the skin and secrete inflammatory and vasoactive chemicals that ensure an influx of inflammatory cells and prevent clotting. Tick bites produce local irritation, predispose bite areas to infection, and can lead to tick paralysis. Moreover, ticks may introduce *Rickettsia rickettsii, Borrelia burgdorferi, Anaplasma phagocytophilum,* and *Ehrlichia canis* into their hosts. The major concern for ticks as a public threat is that domestic animals can bring ticks into houses, where they may quest and feed on people, especially children. The common ticks that bite cats are *Ixodes scapularis* east of the Rocky Mountains, *Ixodes pacificus* on the west coast, *Dermacentor variabilis, Dermacentor andersoni, Dermacentor occidentalis, Amblyomma americanum, Amblyomma maculatum,* and *Rhipicephalus sanguineus,* although all of these ticks are more common on dogs than cats. Adult hard ticks feed for 2 to 5 days most frequently in and around the ears and axillae. Invariably,

tissue trauma accompanies removal of ticks, or fully engorged ticks drop off the cat and seek a suitable microenvironment to lay eggs. Such environments are moist, dark, and protected by leaf litter (usually in a home, no microenvironments are moist enough and the tick dies, although *R. sanguineus* ticks sometimes can find suitable locations in and near kennels). The larvae emerge months later to seek rodents, birds, or reptiles to feed upon, depending on the tick species.

Population management of these tick species depends largely on identification of infested cats, elimination of ticks (by use of topical acaricides or manually removing the ticks), and evaluation of cats for evidence of tick-borne pathogens such as ehrlichiosis and Lyme disease. The only tick with a complete peridomestic life cycle (i.e., that will complete all three molts on dogs or cats) is *R. sanguineus*. Even if any of the other tick species laid eggs in the cattery environment, none could complete its life cycle without access to wildlife hosts for immature tick stages. If *R. sanguineus* is present, ticks should be eliminated from the environment by cleaning and drying up moist crevices and applying acaricides in areas where ticks could hide. For on-cat systemic treatment, the safest acaricide is fipronil.[6] Environmental treatment, most importantly for *R. sanguineus,* can be achieved with cyfluthrin or permethrin.[6]

Mange Mites

Mange is a clinical condition involving inflammation, pruritus, and hair loss, caused in different host species by several species of mite. Because human mange occurs most commonly from infestation with the mite *Sarcoptes scabiei,* the condition in people often is described as scabies. Feline (and occasionally human) mange is caused by the astigmatid mite *Notoedres cati*. These mites are acquired from contact with other infected animals or contaminated environments, tunnel through the skin, and deposit eggs and feces. Larvae hatch from eggs 3 to 5 days after being laid, then burrow side tunnels in the skin off the original tunnel made by the adult. After two nymphal molts, adult mites emerge approximately 17 days after eggs are first laid. *Notoedres* mites cannot tolerate dry environments and survive only a few days off cats.

Notoedres mites cause intense immune-mediated host reactions and pruritus even in small numbers. Usually the mite burrows are found on pinnae or the neck, and to a lesser extent the face, feet, and entire body in severe cases. The infested cat may become so uncomfortable that it traumatizes itself and stops eating. Lesions appear alopecic, thickened, crusted, and exudative; they progress to proliferative production of subcutaneous connective tissue as a result of self-trauma. The skin then is susceptible to secondary bacterial and fungal infections. Scabies mites can infest other host species including bobcats and, transiently, human beings. People infested with the mite may develop reddened pruritic lesions, which can be difficult to diagnose unless the physician has the historical information of exposure to a cat with mange.

If multiple cats in a cattery present with intense pruritus, weight loss, and dermatopathy, mange should be suspected. Unfortunately, affected cats may host a small number of mites, so repeated skin scrapings may be necessary to detect the parasites. If mange is suspected, a miticide trial *of all cats in the population* may help confirm the diagnosis while simultaneously eliminating the problem.

RESPIRATORY DISEASE

In catteries and other dense cat populations, respiratory tract disease almost always reflects nonzoonotic problems such as calicivirus or herpesvirus infection, asthma, bacterial pneumonia, or one of several miscellaneous problems (e.g., foxtail migration, lungworm infestation, and others). However, a rule-out list should contain several dangerous zoonoses for which cats may serve as sentinels of human risk, including tularemia and plague.

Francisella tularensis

Tularemia, also known as rabbit or deerfly fever, is a relatively rare disease in the United States in cats, dogs, and human beings. It results from infection with the small gram-negative bacterium *F. tularensis.* Biotype A *(tularensis)* is present only in North America, is highly virulent, and is maintained in nature by hare reservoirs via *Dermacentor* spp. and *Amblyomma americanum* tick vectors. Biotype B *(palearctica)* occurs most commonly in Europe and Asia but also is present in the United States, is less virulent than biotype A, and is spread by ticks, mosquitoes, deerflies, water, and direct exposure to one of hundreds of possible infected host species.[7] This second biotype is likely to remain viable for months in water, mud, soil, and carcasses.

People with tularemia may have fever, headache, muscle pain and malaise, a maculopapular rash, and hepatolymphadenomegaly. Several clinical forms of human tularemia exist, including ulceroglandular tularemia manifest as pruritus, skin ulcers and lymphadenopathy, oculoglandular tularemia, oropharyngeal, and pulmonary and typhoidal forms with predominantly respiratory and gastrointestinal signs, respectively. Diarrhea in typhoidal tularemia typically becomes bloody and is accompanied by fever and splenolymphadenomegaly. Cats, which acquire tularemia typically by exposure to or eating infected prey, may develop no clinical signs or develop any of the human clinical forms except oculoglandular, and the disease may be fatal in cats. Infected cats typically have fever, purulent ocular and nasal discharge, possibly lymphadenopathy of the nodes draining the site of inoculation, hepatosplenomegaly, oral ulcers, and bacteremia and abscessation of multiple internal organs.[8]

The progression of tularemia to disease and death occurs because of the capacity of the bacteria to proliferate intracellularly within monocytes and neutrophils, induce cytokine responses directly because of the intracellular infection, and initiate endotoxic shock cascades. *Francisella tularensis* is one of the most infectious bacteria to human beings. It produces bacteremia and disease in people after doses of inoculum reportedly as low as 50 to 1000 bacterial organisms, although cats appear to be more resistant.

Infected cats probably are the most likely domestic animal to serve as sources of human infection and important sentinels for human health risk. Few population-based studies of feline exposure to *F. tularensis* have been performed, but a seroprevalence of 7 per cent was detected in one survey in Oklahoma.[8] Cases, often ulceroglandular, of human disease have been described after bites and scratches from, in addition to casual contact with, infected cats.[8,9] In at least two cases, tularemia was acquired by veterinarians, once through a cut on the finger during an ovariohysterectomy on an infected cat.[8]

The risk in veterinarians appears to be increased substantially over the general public, with a fourteenfold higher prevalence reported in one survey of veterinarians compared with a control group of people.[10] Cats with fever, lymphadenopathy, possibly skin ulceration, or nonproductive cough should be evaluated for tularemia, even if the possibility is remote. If one cat is found infected, this one cat represents an important risk to itself, other cats, and human beings. However, if more than one cat has tularemia, the possibility of an outbreak could be considered a public health emergency.

To assess cats for tularemia, testing might include serology for evidence of exposure or culture of suspect tissues on media containing cysteine (e.g., brain heart infusion with blood). Serological results of at least 160 suggest active infection in a cat.[11] The organisms have a characteristic bipolar staining pattern, and the identification can be confirmed in public health laboratories by fluorescent antibody reactions. Any laboratory to which suspect samples are submitted should be alerted to the possibility of tularemia as a diagnosis. In the cattery, cats with suspect tularemia should be isolated and handled by trained staff employing universal precautions. If cats are to be treated, drugs of choice include gentamicin, tetracycline, and chloramphenicol.[8] Infections should be reported to local county or state public health departments, and infected cats should not go into private homes until (or if) completely cleared of infection. Cats that die or are euthanized with suspected tularemia should be necropsied at public health facilities, which may reveal organ enlargement with miliary and raised necrotic foci; lesions should be cultured or evaluated by direct fluorescent antibody. To prevent infections in cats, arthropod control is important, and cats should not be exposed to uncooked meat or other products from rabbits or hares.

Yersinia pestis

Cats are uniquely susceptible to pneumonic plague and represent important sources of infection to human beings and important possible sentinels for sylvatic or terrorist-source plague epidemics. The agent of plague, *Y. pestis,* is a non–spore-forming, facultatively anaerobic, gram-negative bacterium in the family Enterobacteriaceae. Sylvatic plague is maintained in nature primarily in rodent hosts such as prairie dogs, ground squirrels, woodrats, and voles, among which it can spread via fleas or through aerosol discharge of heavily infected animals. In the United States, plague occurs sporadically in the eastern Sierra Nevada mountains, transverse mountain ranges of southern California, and Four Corners areas of Colorado, New Mexico, Arizona, and Utah, into Texas, Oklahoma, and Kansas.

Cats, which have a 33 per cent mortality rate resulting from plague,[12] acquire the infection through direct exposure to infected wild rodents or their fleas. Human beings acquire plague via fleas (bubonic plague), direct exposure to respiratory secretions of other infected persons (pneumonic plague), or cats. Infected cats, like people, display the bubonic, pneumonic, and septicemic forms of plague and develop bacteremia and high levels of infection in the oropharynx from 1 to 10 days after exposure. Mandibular and retropharyngeal lymph nodes become enlarged and eventually abscessed. Infection can spread to the lungs (pneumonic plague) or other organs where abscesses may develop, or the *Y. pestis* endotoxin can cause septic shock, disseminated intravascular coagulation (DIC), or death. The pathological lesions in feline plague are similar to those in human beings with pneumonic plague.[13]

Experimental work has documented that cats can acquire plague through prey. After 16 cats were fed whole, infected rodent carcasses, it was speculated that trauma associated with sharp bones could have facilitated infection because mandibular and sublingual lymph nodes were enlarged and *Y. pestis* was recovered early from oropharyngeal lymph nodes.[14] Of the cats that became infected, 6 died of fulminant systemic disease within 9 days, whereas the remaining 7 became ill but recovered. All cats developed elevated rectal temperature, positive blood and throat cultures, neutrophilia, and lymphopenia, and seroconverted unless they died before onset of detectable antibodies. Interestingly, of the cats that survived, early clinical signs appeared very similar to those seen in cats that died, including lymphadenopathy, neutrophilia, lymphopenia, and positive blood cultures. However, on day 4, cats in this group defervesced and eventually developed high serological titers.

In endemic areas, cats with fever, lymphadenomegaly, pneumonia, or nonspecific systemic illness should be evaluated for plague, tularemia, or mycobacteriosis. Not only is it important to provide medical care for cats, but it is also crucial to manage the risks to human beings. Cats may bring active infection into homes via infected fleas and via shedding of the bacterium from the oral cavity.[15] Between 1977 and 1998, 23 human cases, representing 7.7 per cent of the 297 cases reported in that period, were associated with exposure to domestic cats, including 5 fatal cases.[15] One important emerging risk factor for pneumonic plague, particularly as an occupational hazard, is exposure to infected cats, because only 2 of 228 human patients without cat exposure acquired plague through inhalation compared with 5 of the 23 patients with cat-associated cases ($p < 0.0001$).

For diagnosis of plague, fine-needle aspirate, cytology, and culture of lymph nodes, or culture of swabs of the throat, often yield the diagnosis. However, confirmation of the diagnosis likely will take days to weeks, so cats must be managed appropriately in the meantime. Cats should be isolated and treated to remove fleas. Personnel working with plague-suspect cats should be careful to employ universal precautions particularly against saliva and respiratory secretions. The suspicion of plague should be reported to local health authorities, who likely will perform further testing of in-contact cats and people. First-line antibiotics for infected cats include tetracycline, chloramphenicol, and gentamicin,[16] although antibiotic-resistant strains of *Y. pestis* have been detected in Africa.[17] Cats should not be released to their owners until fully recovered and documented clear of infection by culture or PCR.

REDUCED FECUNDITY

Coxiella burnetii

Coxiella burnetii is a gram-negative, spore-forming rod that is the causative agent of Q fever. Infection occurs most commonly in sheep, goats, cattle, cats, and to a lesser extent, human beings. *C. burnetii* appears to be maintained by a tick-wildlife cycle. For example, in rural parts of Montana where little or no exposure to livestock or human beings occurs, *C. burnetii* has been recovered from wild rodents, which indicates a possible sylvan reservoir.[18] Ticks are thought to be the primary vector for transmission among animals including people. *Dermacentor* spp., *R. sanguineus,* and *Amblyomma* spp. are the ticks implicated most often as vectors of *C. burnetii*. Although

Ixodes scapularis and *Ixodes pacificus* are not associated with Q-fever in the United States, *Ixodes ricinus* ticks in Austria recently have been shown to be carriers.[19] *C. burnetii* is distributed essentially worldwide. Its seroprevalence in cats ranges from 16 to 20 per cent in the United States, Canada, and Japan.[20]

Most infections in human beings are acquired either by tick bite or through direct exposure to contaminated discharges (typically vaginal during abortion) from animals. During infection, *C. burnetii* targets and reproduces in pulmonary epithelial and endothelial cells, leading to vasculitis and pneumonitis. Acute Q fever in humans is a febrile, influenza-like illness, often with pulmonary and hepatic involvement. Chronic Q fever is characterized by chronic endocarditis and hepatitis.[21] Type 4 immune complex disease occurs occasionally as a sequela of *C. burnetii* infection, resulting in inflammation in joints, kidneys, and the anterior chamber of the eye. Most infections in cats are subclinical, although fever and lethargy were documented in experimentally infected cats.[22] Abortion also is a potential outcome in *C. burnetii*–infected queens.

The main concern for *C. burnetii* infection in cats relates to its risk in human health. Multiple cases of human Q fever recently have been linked with exposure to parturient cats. The bacterium is shed in high numbers in parturient fluids and tissues such as the placenta and amnion, and human infection occurs after ingestion or inhalation of these infective materials.[23] Cats may shed the bacterium in urine, milk, and feces for a month or more after infection. A human outbreak of Q fever in Nova Scotia was seen after exposure to a parturient cat.[24] Another outbreak in 16 people was presumed to have originated from exposure to *C. burnetii* spores on the clothing of a coworker who cared for an infected cat with newborn kittens.[25] Because cats can be a source of exposure to human beings, veterinarians should be aware of the potential for *C. burnetii* infections.

Diagnosis of *C. burnetii* infection in cats can be difficult because Q fever usually is subclinical. Serology (including ELISA and IFA) to test for fourfold rising titers most often is used to identify cats that have been exposed to *C. burnetii*. PCR from blood or tissue of actively infected cats also is a potential tool for diagnosis.[26,27] Treatment of *C. burnetii*–positive cats is indicated to help reduce the risk of human exposure and can be accomplished by the use of antibiotics. Tetracycline, chloramphenicol, and erythromycin each have been shown to be effective and should be administered for 2 to 4 weeks.[20] Prevention of *C. burnetii* requires decontaminating environments where disease has occurred, eliminating ticks, and reducing exposure to infected hoofstock. Bleach, ultraviolet light, heat, and desiccation do *not* kill *C. burnetii* spores, although 100 per cent ethanol applied for 30 minutes and allowed to evaporate will kill the bacteria.

SYSTEMIC INFECTIONS WITH AND WITHOUT CLINICAL PROBLEMS IN CATS

Cats are susceptible to several systemic vector-borne pathogens that can, although rarely do, cause clinical disease. These include *Ehrlichia canis* and *Ehrlichia ewingii* (canine monocytic and granulocytic ehrlichiosis), *Anaplasma phagocytophilum* (formerly *E. equi* or the canine granulocytic ehrlichiosis agent), *B. burgdorferi* (Lyme disease), *R. rickettsii* (which causes Rocky Mountain spotted fever), and *Bartonella* spp. infection. Although tick exposure may be a population problem, the manifestation and management of any of these diseases would likely be an individual cat problem.

E. canis is the most common ehrlichial agent found in clinically ill dogs and has been reported occasionally in cats. It is closely related to, but distinct from, *Ehrlichia chaffeensis,* the agent of human monocytic ehrlichiosis, although a case of human disease was reported in Venezuela in a patient infected with *E. canis*. This infection, transmitted by the tick *Rhipicephalus sanguineus,* targets the macrophage, producing fever, lymphadenopathy, anemia, and thrombocytopenia in its early stages. Persistently infected animals eventually may enter a late stage of ehrlichiosis characterized by systemic disease, bone marrow suppression, and pancytopenia. Late-stage ehrlichial infection produces lethargy and weight loss, lymphadenomegaly and splenomegaly, uveitis and retinitis, and bleeding from eyes and nose. Monocytic ehrlichiosis has been observed in cats.

In some areas of the United States, such as New England, the upper Midwest, and California, granulocytic anaplasmosis (GA), formerly granulocytic ehrlichiosis (GE), is more common than monocytic ehrlichiosis. This disease, caused by *A. phagocytophilum,* is vectored by the Pacific black-legged tick, *I. pacificus,* or the deer tick, *I. scapularis.* The agent of GA also infects people, horses, and a range of wildlife species. The clinical signs in most hosts include fever, muscle and joint pain, and headache in people. Hematological and biochemical abnormalities may include thrombocytopenia, anemia, leukopenia, and elevated liver enzymes. However, in all species, most infections do not manifest any abnormal signs and go unnoticed. In a recent case of naturally occurring GE in a cat from Sweden, fever, left-shifted neutrophilia, and ehrlichial inclusions were present in 24 per cent of the neutrophils.[28] The titer was 5120, the cat was PCR-positive, and DNA sequencing indicated 100 per cent homology between this isolate and GE from local dogs and horses. Cats have been shown to be susceptible to disease as a result of GA by experimental infection, with more severe disease in cats coinfected with feline immunodeficiency virus (FIV).[29]

Ehrlichiosis and anaplasmosis are diagnosed by direct visualization of the organism in target cells (usually performed by clinical pathologists), serology, and PCR. *E. ewingii,* which is closely related to *E. canis*, may be seen in neutrophils as can *A. phagocytophilum,* within small cytoplasmic, membrane-bound vacuoles called morulae. If monocytes contain morulae, these could be *A. phagocytophilum* or *E. canis.* The sensitivity of this assay is increased if a buffy coat smear is examined. PCR is one of the most sensitive tests available for active ehrlichiosis and anaplasmosis, because acute infections, especially with granulocytic anaplasmas, often are resolved before the animal seroconverts. Serology is useful for documentation of previous exposure to an ehrlichia/anaplasma, fourfold rises in titer retrospectively, or possible chronic infection with *E. canis.* Because of weak cross-reactivity between granulocytic and monocytic ehrlichiae, it is best to run both titers, because typically one is much higher than the other.

Acute ehrlichiosis and anaplasmosis usually respond well to treatment with doxycycline.[30] Defervescence usually occurs within 24 hours. Even without treatment, most cases of GA resolve on their own within about a week. In contrast, chronic monocytic ehrlichiosis is not treated easily and has a poor prognosis. Even after treatment of dogs with chronic ehrlichiosis

with anti-ehrlichial drugs (doxycycline or imidocarb), fluids and/or blood products, possibly erythropoietin or granulocyte colony-stimulating factor, and corticosteroids, the prognosis is only fair in many cases. The extent to which cats develop chronic ehrlichiosis is unknown, and no treatment trials have been performed, but treatment comparable to dogs probably is the optimum choice for cats.

B. burgdorferi, the spirochete that causes Lyme disease, is transmitted by the same *Ixodes* spp. ticks as GA. It induces mild, nonspecific to severe disease in infected dogs and people, including severe, chronic arthritis and neurological and cardiac dysfunction. Dogs can develop severe nephritis with protein-losing glomerulopathy and fatal renal failure. Because the spirochete can reside in skin and connective tissue, the infection may last months to years.

Some evidence exists that cats are exposed to Lyme disease but probably do not develop severe disease. Previous studies have shown seroprevalence in cats from 5 to 36 per cent, up to 71 per cent using a sensitive and specific C6 ELISA in a Lyme hyperendemic region.[31,32] Experimental *B. burgdorferi* infection in cats was associated with fever, stiffness, arthritis, hepatic, gastrointestinal, and neurological disease.[33] Naturally infected cats have cycling IgG and IgM levels suggesting possible persistent, reactivating disease.[33]

Cats (and dogs) with chronic or severe arthritis, fever of unknown origin, or other consistent signs in Lyme endemic areas should be screened for exposure to *B. burgdorferi.* A two-step process should include screening by IFA or ELISA, followed by Western blotting, because IFA alone has a high rate of false-positive reactions. A newly marketed C6 ELISA appears to have good sensitivity and specificity.[32] Western blot can discriminate exposure to field strains from vaccination. Culture or PCR may be positive especially in joint fluid, which confirms the diagnosis. Appropriate therapy for cats is not known but doxycycline, amoxicillin, or azithromycin would be good choices. Whether canine Lyme vaccines are useful or necessary for cats is unknown.

The pathogen responsible for Rocky Mountain spotted fever (RMSF) is *R. rickettsii,* a bacterium transmitted by the ticks *Dermacentor andersoni* and *D. variabilis. R. rickettsii,* like other spotted fever rickettsiae, is maintained in ticks transstadially and transovarially, which allows for ticks to contribute to the reservoir capacity in nature.[34] Other reservoirs include numerous wild mammals and dogs. Cases in human beings and animals are uncommon west of the Rocky Mountains, but continue to emerge in the American Southeast.

R. rickettsii is inoculated into a mammalian host via the bite of an infected tick. It invades endothelial cells and leads to vasculitis, which causes especially severe lesions in skin, brain, heart, and kidneys. Classically, edema develops 2 to 10 days after the tick bite. Skin lesions may range from vesicular, hyperemic lesions to severe necrosis. Mucosal, genital, and retinal petechiae and hemorrhages may occur. Ultimately, shock and central nervous system disease can be fatal. Dogs are susceptible to severe RMSF, but cats are reported to be incidental hosts.[35] Antibody testing (especially with a fourfold rise in titer) may confirm exposure in cats to RMSF retrospectively. However, a low to moderate positive IgG titer does not confirm active infection, because many animals may be seropositive and the antibodies cross-react with all spotted fever group rickettsiae (but not typhus group). If indicated, treatment should be initiated without waiting for confirmation of diagnosis. Appropriate antibiotics include tetracycline, enrofloxacin, and chloramphenicol. Prevention depends on tick control. Infection typically does not spread to dogs or staff, but prevention of environmental contamination of the peridomestic tick *R. sanguineus* is important.

Other rickettsial zoonotic pathogens that also may infect cats with few or no clinical signs include *R. felis*, *R. typhi*, and *R. akari*. *R. felis* and *R. typhi* are rod-shaped, gram-negative bacteria in the rickettsial typhus group. *R. typhi* causes murine typhus (MT), while *R. felis* causes murine typhus-like syndrome (MTLS) in human beings. Both are transmitted by fleas (the cat flea *Ctenocephalides felis* or the Oriental rat flea *Xenopsylla cheopis*) via a bite or by inoculation of an open lesion or mucous membrane with infected flea feces.[21] The main reservoir for *R. felis* appears to be the North American opossum *(Didelphus virginianus),* whereas rats of the genus *Rattus* form the likely reservoir for *R. typhi.*[36] *R. felis* appears to be distributed throughout North America with seroprevalence in cats ranging from 8 to 20 per cent overall[37]; particularly high rates have been documented in southern California, southern Texas, and Oklahoma.[38] *R. typhi* previously has been reported to have a worldwide distribution with a significant prevalence in the United States. However, more likely is that its true geographical distribution is limited to warmer climates such as Africa, Asia, and certain parts of Europe. Studies that previously have identified *R. typhi* in the United States more likely were identifying *R. felis*.

The major significance of *R. typhi* and *R. felis* is their ability to cause disease in human beings. MTLS and MT are associated with low mortality rates (case fatality ratios of 0 to 1 per cent) and generally are self-limiting infections.[21] After flea exposure and inoculation of *R. felis* or *R. typhi* into a bite wound or other susceptible tissue, infected individuals experience high fever, headache, nausea, and a generalized maculopapular rash after a 1- to 2-week incubation period.[21] Cats do not show outward clinical signs of typhus, and it is not known whether any pathology exists in cats associated with these infections. However, cats do seroconvert after exposure to *R. felis* and *R. typhi* and thus may represent an important indicator of infection and potential for human disease caused by these agents.

Diagnosis of *R. felis* and *R. typhi* infection in human patients usually is based on clinical signs, history of exposure to a flea bite or travel to a high risk area (such as a known urban focus or an animal shelter). Clinical diagnosis usually is confirmed by serology, either by ELISA or IFA (immunofluorescent antibodies). Identification of pathogen-specific DNA also can be performed using PCR.[38] In cats, serology can be useful for identifying exposure but cannot identify active infections. Prevention of *R. felis* or *R. typhi* infection in cats and people is best accomplished by effective rodent and flea control.

R. akari belongs to the spotted-fever group of Rickettsiae. The reservoir for *R. akari* is the domestic house mouse (*Mus musculus*) and human rickettsialpox is transmitted via the bite of *Liponyssoides sanguineus,* a common mite parasite of the domestic mouse. Human rickettsialpox was first diagnosed in New York City in the 1940s and is endemic in that area because of the large numbers of house mice. Human cases of rickettsialpox generally present with mild fever, headache, and maculopapular rash and are associated with low morbidity and mortality.[23] Recently dogs from New York City were reported to be seropositive for *R. akari.*[39] Although the occurrence and

prevalence of *R. akari* in feline populations are unknown, cats in high-density populations such as shelters and catteries have the potential to be exposed to mice and their ectoparasitic mites, and possibly *R. akari.* Diagnosis usually is based on clinical signs, serology, and possibly PCR.[38]

Probably the single most common vector-borne infection of cats is bartonellosis and cats serve as the main reservoirs of this disease to human beings (see Chapter 4). *Bartonella henselae* infection is common in cats, transmitted among cats by fleas.[40] Evidence for this bacterium has been detected by PCR or culture in 11 per cent of French cat fleas[36] and 4 to 70 per cent elsewhere.[41] *Bartonella clarridgeiae* infection also has been detected in 70 per cent of French cat fleas by PCR[36] and appears more common in European than North American cats. The role of cats and fleas in *Bartonella quintana* epidemiology is unclear: the accepted vector is the human body louse *Pediculus humanus* and the reservoir supposedly human beings. However, exposure to cat fleas was a risk factor for several cases of human trench fever[42,43] and *B. quintana* DNA was amplified in 17 per cent of French cat fleas.[36]

The greatest significance of bartonellosis in a cattery is the maintenance of a reservoir for human disease. *B. henselae* and *B. clarridgeiae* are the agents of cat-scratch disease lymphadenopathy in human beings (particularly children), in addition to bacillary angiomatosis, relapsing fever, bacillary peliosis, and meningitis/neuroretinitis most significantly in immunosuppressed people. *B. henselae* and *B. quintana* have been detected in cases of human endocarditis.[44] Diseases such as cat scratch disease and bacillary angiomatosis usually are either self-limiting or respond well to antibiotics, but chronic sequelae sometimes do occur, such as relapsing disease and encephalitis.[45] Many cases of cat scratch disease in people appear to be linked to cat bites or scratches, whereas others are related to flea bites. Trench fever resulting from *B. quintana* continues to emerge particularly among urban homeless, with risk factors including body louse infestations and alcoholism.[23] Cats infected with *B. henselae* or *B. clarridgeiae* may remain infected for months to years yet usually remain clinically well, although anemia, fever, lymphadenomegaly, neurological dysfunction, and reproductive disorders have been reported following experimental infection.[46,47] Stomatitis, urinary tract infection, uveitis, endocarditis, myocarditis, nephritis, and other problems have been reported rarely in naturally infected cats.[20]

To evaluate risks to human beings of bartonellosis from a given cat population, several diagnostic strategies may be employed. Diagnosis of active bartonella infection can be made by blood culture or PCR, although many laboratories do not offer the specialized techniques required for obtaining positive culture. Serological tests indicate whether a cat or dog has been infected previously but often are positive in most or all cats in a cattery, which limits their usefulness. Management of bartonellosis in catteries must include excellent flea control, minimization of bite and scratch wounds to persons (primarily through staff training), counseling of potential owners (especially if immunosuppressed) with regard to risks, and possibly antibiotic treatment. However, although several different antibiotics have been proposed to clear the bacteremia associated with *Bartonella* spp. infection, including tetracycline, amoxicillin-clavulanate, enrofloxacin, erythromycin, and rifampin, none resolves 100 per cent of feline infections. Given that a cat infected with *B. henselae* probably will remain well, the main justification for treatment is to prevent human infections, which also can be accomplished by careful matching of a possibly infected cat with an appropriate home that does not contain elderly people, young children, or known immunocompromised individuals. The reader is referred to Chapter 4 for a detailed discussion of *Bartonella* infections in cats.

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Chapter 76

Recognition and Management of Stress in Housed Cats

Brenda Griffin and Kelly R. Hume

"He who grabs a cat by the tail learns a lot about cats."
—Mark Twain

WHAT CATS ARE AND WHY

To understand the feline stress response and to truly appreciate the importance of minimizing it, one must first examine physiological and behavioral characteristics of cats and why they are unique compared with most other domestic species. The domestic cat (*Felis catus*) descended from the African wildcat (*Felis libyca*), and the two species remain closely related. Feline domestication was accomplished relatively recently and passively compared with that of other species, occurring approximately 5000 years ago, compared with 20,000 years for dogs.[1-4]

Human beings did not seek to conquer or "tame" cats, rather the cat-human relationship began as a commensal one and became mutualistic. As the ancient Egyptian civilization developed, cats began to associate with people. Egypt's first permanent settlements with their granaries and silos provided a unique concentration of rodents and other edibles that attracted wildcats.[1-4] The value of their hunting abilities was recognized and greatly respected, and cats were welcomed and revered for guarding valuable stores of grains. To the Egyptians, the presence of cats was a grace and they worshipped them for what has been described as their "aura of power."[5] Cats could kill poisonous snakes skillfully, see in the dark, and reproduce prolifically, and they possessed free and independent spirits.

In contrast to other species, domestication changed few of the cat's structural and behavioral characteristics, and they have retained many of the instincts of their wild predecessors.[1-4] Cats are true carnivores and are designed nearly perfectly as predators.[1,2] They are equipped to sense and avoid danger and are hardwired physiologically for escape or defense and possess heightened fight-or-flight responses.[6] Cats possess superb balance, flexibility, and the abilities to either conserve or explode with energy.[1] They are uniquely agile, capable of precise pouncing, calculated sprinting, and vertical jumping and climbing. In addition, cats have astonishing sensory capabilities including specialized eyesight highly sensitive to movement and functions at low light levels (when their usual prey, rodents, are most active).[1,5,7] Their sense of hearing extends into the range employed by bats such that cats are capable of detecting high-frequency chattering of rats and mice.[7] They also possess particularly keen senses of smell and touch, with their specialized whiskers and sensitive guard hairs in addition to many other unique senses and abilities, including their "homing ability" and righting reflex.[1,7]

Today, domestic cats possess a variety of lifestyles and levels of tractability ranging from the most docile, sociable housecat, to free-roaming, unsocialized feral cats that will not allow handling.[5] They are richly complex creatures whose behavioral needs and responses frequently remain underrecognized or misunderstood. Additional information on behavior can be found in Chapter 71.

THE STRESS RESPONSE

Stress Defined

Stress involves outcomes secondary to increased secretion of catecholamines or to activation of the hypothalamic-pituitary-adrenal (HPA) axis, and includes both physiological adaptations as well as emotional ones.[8-11] Not all stress responses are harmful; in fact, stress is a normal part of life and a certain level of stimulation is rewarding and necessary for health. In the

context of this chapter, stress is used to refer to an abnormal or extreme adjustment in physiology and/or behavior in response to prolonged or intense aversive stimuli.

Physiology of the Stress Response

The stress response is complex and involves an array of neuroendocrine responses of which two main pathways have been elucidated. One pathway of response involves activation of the sympathetic branch of the autonomic nervous system, which triggers release of epinephrine and norepinephrine from the adrenal medulla.[8-11] These are the hormones associated with the classic "flight-or-flight" response of acute stress, which prepares the body for defense or escape. Heart rate, cardiac output, and blood pressure are increased, while glucose is released from the liver, blood is shunted to the central nervous system and muscles, and respiratory bronchioles dilate. Although catecholamine release can be triggered by a wide variety of stimuli, apprehension is the most potent stimulus for its release in cats.[12] Sympathetic adrenomedullary activity normalizes typically once a stressor ceases.

If a stressor persists, the hypothalamic-pituitary-adrenal (HPA) response pathway also is activated, resulting in glucocorticoid secretion. At basal concentrations, glucocorticoids help to maintain blood glucose and hepatic glycogen concentrations, cardiovascular function, blood pressure, muscle work capacity, and renal function, while exerting permissive effects on many other hormones and mediators.[12] In the presence of a chronic stressor, glucocorticoid secretion decreases over time; however, a greater sensitivity to novel stressors persists. Introduction of a novel stressor to a chronically stressed animal results in an increased rate of adrenocortical response and an overall increased responsiveness of the pituitary-adrenal system.

Temporary activation of these stress response pathways generally is of benefit to the animal or at least of no pathological consequence. However, in some instances acute stress in cats can have devastating effects. For example, in cats with severe cardiopulmonary compromise, severe acute stress can result in fulminating heart failure and death.[12] Cats with hyperthyroidism are particularly prone to negative effects of acute stress because they have increased numbers and up-regulation of epinephrine receptors.[13]

The harmful effects of chronic activation of these pathways have been well described. Long-term activation of the HPA axis and cortisol secretion can elicit adverse metabolic responses that promote dehydration, mental depression, insulin resistance, and susceptibility to infection, in addition to peptic ulcers, decreased reproductive capacity, and sudden death.[9,11,12] Chronic stress also can alter metabolism sufficiently to cause weight loss, prevent normal growth, and result in abnormal behavior deleterious to the animal.[9] Increased endothelial and epithelial permeability secondary to stress response pathways may affect pathology in diseases of the urinary bladder (see Chapter 47), gingival tissues, skin, lung, and gastrointestinal tracts.[14]

Stress responses and immunity also are intimately related and stress compromises the immune response, which lowers resistance to infection.[15] Stress also may trigger shedding of certain viral pathogens. For example, stress can reactivate latent herpesvirus infections in cats. In fact, simply moving housed cats from one room to another can precipitate shedding of the feline herpesvirus (see Chapter 77).[16]

Feline Stressors

A stressor represents any stress-producing factor or stimulus.[11] Housing cats whether in veterinary hospitals, animal shelters, boarding or quarantine facilities, research laboratories, or breeding catteries presents enormous opportunities for introducing stressors and inducing stress. Stressors in cats may include illness, captivity, transport, drafts, changes in environmental temperature, light pattern and/or ventilation, overcrowding, isolation, strange smells, noises, dogs, other cats, diet changes, handling, restraint, irregular caretaking schedules, unpredictable daily manipulations, the absence of familiar human contact, and the presence of unfamiliar human contact.[6,12,14,17-20] Even the odor of a commonly used veterinary product (such as isopropyl alcohol) can be a potent stressor. In fact, anything unfamiliar to a cat can trigger apprehension and activate the stress response.

Factors Affecting the Stress Response

Certain characteristics of the stressor can influence the stress response. These include severity, chronicity, novelty, predictability, and duration.[9,10,15,21] The perception of the individual also affects the stress response. In cats, perception of stressors may be influenced by genetics, personality, and prior socialization and experience.[9,19,22] Poor nutrition can compound the physiological effects of stress, and the effects of multiple stressors may be cumulative.[9,11,15]

Coping is the act of lessening the negative impact of a stressor.[6,21] It involves performance of a behavior that alters the stressor or the emotionality associated with it. Examples of behavioral coping strategies include hiding or escaping, seeking social companionship, and acquiring mental stimulation.[21] The ability to cope correlates strongly to the physical and mental impact of the stressor on an individual.[6,21] Just as in other species, marked variability occurs among individual cats regarding their ability to cope.

When aversive stimuli are unpredictable, chronic fear and anxiety may result. Conversely, predictable aversive events allow a period of calm and comfort between stress responses.[21] Provided the intensity of the aversive stimulus is not too great and that coping strategies are implemented, stressors previously novel and unpredictable become familiar and routine over time, which results in adaptation and cessation of the stress response pathways.[8]

Psychological stressors unique to housed cats often originate from the lack of opportunities for active behavioral responses that would serve as means of coping. The degree of behavioral control a cat has over an aversive stimulus is a major determinant of its impact. When a stressor is perceived as inescapable or uncontrollable, the resulting stress response is most severe.[6,21] This is an extremely important consideration in the design of housing and husbandry protocols for cats.

Methods to Measure Stress in Cats

Analyses of behavior changes and physiological measures (such as changes in cortisol secretion or heart rate) have been used to identify physiological stress in many species, including

cats. A combination of behavioral and physiological or biochemical criteria is best, because single variables can be ambiguous and potentially misleading.[23] The importance of noninvasive measurement is self-evident to protect animal welfare and to avoid disturbing the system under observation. Restraint or even observation may provoke stress responses. Indeed, the "white coat effect" is well recognized.[23] This may be particularly applicable to cats. For example, in a study of normal cats fitted with radiotelemetry implants to measure arterial blood pressure, significant increases in blood pressure were observed whenever laboratory personnel were present.[24]

A number of methods of assessing stress in housed cats have been evaluated. Adrenal responses of cats to physiological stressors can be assessed by measuring urinary cortisol concentrations[25] or by measuring cortisol metabolites in the feces.[26] Use of serum cortisol measurements is not recommended and was found to be unreliable in a study of kittens.[27] Several authors have described behavior assessment of stress in domestic cats.[18-20,28-30]

Studies Assessing Stress in Housed Cats

Over the past decade, researchers have sought to better understand the biological and psychological impact of novel environments on cats to minimize their stress and optimize their care when they are confined outside of their "home" environments in a variety of settings. A review of these studies provides useful insights in the context of this chapter.

Stress was evaluated in 16 singly caged laboratory cats using urine cortisol measurements and response to ACTH, in combination with constant video surveillance during a 3-week study period.[6] The cats were divided into two groups of eight cats each: one of the groups received regular caretaking while the other was subjected to altered caretaking characterized by irregular feeding and cleaning times, absence of talking and petting by human beings, and daily unpredictable manipulations (such as being placed in a carrier or being moved to different cage). Unpredictable caretaking and handling were found to be potent stressors, resulting in activity depression and withdrawal behavior. Overcrowding and insufficient hiding places also increased stress. Active exploratory and play behavior was suppressed in stressed cats, and stressed cats spent more time awake and alert and trying to hide. The ability to control aversive stimuli through hiding decreased cortisol concentrations profoundly when measured over time and in response to ACTH. These data indicate that chronic stress can be caused by poor husbandry, and that activity, depression, and withdrawal behaviors are indicators of persistent stress. Furthermore, to promote well-being, caged cats should be provided with appropriate places for concealment. Finally, high levels of exploratory behavior may be an indicator of adaptation.

Another author evaluated urine cortisol concentrations and behavioral data using cameras and time lapse videos in seven cats housed in a quarantine facility for 6 months.[28] The cats were housed singly in runs (2.11 m^2), which were equipped with a resting board and a house containing additional resting platforms. The cats received little human contact during the quarantine period. Based on hormonal and behavioral data, it took approximately 5 weeks for the cats to show adaptation to their environment. They spent most of the first 2 weeks concealed in the house and urine cortisol concentrations were significantly lower during and beyond their second month in quarantine compared with initial measurements. As they adapted, the cats spent less time hiding and more time higher in the run. These findings illustrate that hiding is an important coping mechanism for cats placed in a new environment, and cats possess preferences for high shelves for perching.

Despite signs of adaptation, the cats in this study remained inactive 90 per cent of the time observed, whereas in health, cats are inactive only approximately 75 per cent of the time. As their hiding behavior decreased after the first month, it was replaced by inactive rather than active behavior. This was attributed to the lack of environmental enrichment and human contact experienced by the cats in quarantine. Animals housed in impoverished conditions generally show a gradual decrease in the diversity of their behaviors and acquire an increasingly passive character with lack of interest in their external environment. In a similar study, the same author evaluated stress and adaptation in shelter cats and found that most shelter cats begin to adapt to their environment within the first week. The slower adaptation of cats in quarantine compared with shelter cats was attributed to environmental factors, including the notable lack of human contact experienced by the cats in quarantine.

One author used a behavioral observation scale to evaluate stress in cats in a series of studies in which data collection was based on a 7-level "Cat-Stress-Score" (Table 76-1).[18-20] Scores were assigned based on body postures and ranged from "fully relaxed" (score 1) to "terrorized" (score 7). In a study of stress and adaptation of cats in boarding catteries, single, paired, or group-housing conditions were evaluated in 140 cats during a 2-week stay, compared with 45 control cats that had been housed for several weeks.[18] Overall, the levels of stress based on mean "Cat-Stress-Scores" declined during the 2 weeks of boarding in all study groups, with a pronounced decline over the first 4 days. Neither housing style nor age influenced stress scores. Approximately two thirds of the cats adjusted well to boarding during the 2-week period, whereas boarding remained stressful for the other one third whose mean scores remained higher than "weakly tense" (score 3). These data have important implications and suggest that boarding or hospitalization stays of cats should be avoided or minimized whenever possible.

In a separate study, "Cat-Stress-Scores" were used to evaluate socialization status and stress in cats housed singly and in groups in animal shelters during a 1-week study period.[19] Socialization status towards other cats (conspecifics) and people was determined in 169 rescued cats by means of behavioral tests and owner questionnaires. Cats were determined to be either "cat friendly" (socialized towards conspecifics) or not, and either "people friendly" (socialized towards people) or not. Not surprisingly, "non–cat-friendly" cats were more stressed than "cat-friendly" cats when group-housed, based on mean "Cat-Stress-Scores." In addition, other group members were more stressed when "non–cat-friendly" cats entered the group. For "cat-friendly" cats, differences in stress were not seen between single and group housing in the 1-week study period. Cats that were not socialized towards people remained very stressed during the entire study period; however, some cats required serial evaluations over a period of days before "showing their true colors" and exhibiting "friendly" behavior towards people. These data indicate that for initial short-term stays, individual caging may be preferred to group housing

Table 76-1 | **Cat-Stress-Scores**

SCORE	BODY	BELLY	LEGS	TAIL	HEAD	EYES	PUPILS	EARS	WHISKERS	VOCALIZATION	ACTIVITY
1 Fully relaxed	*i:* Laid out on side or on back *a:* Not applicable	Exposed, slow ventilation	*i:* Fully extended *a:* Not applicable	*i:* Extended or loosely wrapped *a:* Not applicable	Laid on the surface with chin upward or on the surface	Closed or half opened, may be blinking slowly	Normal	Half back (normal)	Lateral (normal)	None	Sleeping or resting
2 Weakly relaxed	*i:* Laid ventrally, half on side, or sitting *a:* Standing or moving, back horizontal	Exposed or not exposed, slow or normal ventilation	*i:* Bent, hind legs may be laid out *a:* When standing legs extended	*i:* Extended or loosely wrapped *a:* Tail up or loosely downwards	Laid on the surface or over the body, some movement	Closed, half opened, or normal opened	Normal	Half back (normal) or erected to front	Lateral (normal) or forward (normal)	None	Sleeping, resting, alert or active, may be playing
3 Weakly tense	*i:* Laid ventrally or sitting *a:* Standing or moving, back horizontal	Not exposed, normal ventilation	*i:* Bent *a:* When standing legs extended	*i:* On the body or curved backwards, may be twitching *a:* Up or tense downwards, may be twitching	Over the body, some movement	Normal opened	Normal	Half back (normal) or erected to front or back and forward on head	Lateral (normal) or forward	Meow or quiet	Resting, awake or actively exploring
4 Very tense	*i:* Laid ventral, rolled or sitting *a:* Standing or moving, body behind lower than in front	Not exposed, normal ventilation	*i:* Bent *a:* When standing hind legs bent, in front extended	*i:* Close to the body *a:* Tense downwards or curled forward, may be twitching	Over the body or pressed to body, little or no movement	Widely opened or pressed together	Normal or partially dilated	Erected to front or back, or back and forward on head	Lateral (normal) or forward	Meow, plaintive meow or quiet	Cramped sleeping, resting or alert, may be actively exploring, trying to escape
5 Fearful, stiff	*i:* Laid ventrally or sitting *a:* Standing or moving, body behind lower than in front	Not exposed, normal or fast ventilation	*i:* Bent *a:* Bent near to surface	*i:* Close to the body *a:* Curled forward close to the body	On the plane of the body, less or no movement	Widely opened	Dilated	Partially flattened	Lateral (normal), forward or back	Plaintive meow, yowling, growling or quiet	Alert, may be actively trying to escape
6 Very fearful	*i:* Laid ventrally or crouched directly on top of all paws, may be shaking *a:* Whole body near to ground, crawling, may be shaking	Not exposed, fast ventilation	*i:* Bent *a:* Bent near to surface	*i:* Close to the body *a:* Curled forward close to the body	Near to surface, motionless	Fully opened	Fully dilated	Fully flattened	Back	Plaintive meow, yowling, growling or quiet	Motionless alert or actively prowling
7 Terrorized	*i:* Crouched directly on all fours, shaking *a:* Not applicable	Not exposed, fast ventilation	*i:* Bent *a:* Not applicable	*i:* Close to the body *a:* Not applicable	Lower than the body, motionless	Fully opened	Fully dilated	Fully flattened back on head	Back	Plaintive meow, yowling, growling or quiet	Motionless alert

i, Inactive; *a*, active.

Reprinted from Kessler MR, Turner DC: Stress and adaptation of cats (*Felis silvestris catus*) housed singly, in pairs, and in groups in boarding catteries. Anim Welf 6:243, 1997, with permission.

unless prior socialization status is known, and that housing feral cats should be avoided because of the high stress levels.

Finally, the effects of density (in enriched group housing) and cage size (in single housing) on stress and adaptation of cats in animal shelters and boarding catteries were evaluated using "Cat-Stress-Scores."[20] Group density was correlated highly with stress level of cats housed in groups, and cats were scored as "weakly tense" (score 3) or higher when the group density reached 0.6 animals/m^2. Therefore, to avoid stress, a group density of 0.6 cats/m^2 should not be exceeded. Cats housed in 0.7 m^2 cages exhibited a higher stress level than cats housed in 1.0 m^2 cages in a 1-week study period, which indicates that cage size may be a risk factor for stress. However, neither the ideal nor minimum cage size to ensure cat well-being could be estimated based on these findings.

Another author used "Cat-Stress-Scores" in combination with measurement of urine cortisol to assess stress in 120 shelter cats housed singly in cages with and without environmental enrichment.[30] Cats were selected randomly and behavioral scoring was performed at three separate time points during a single day. Voided urine specimens were collected on the same day for measurement of cortisol. Environmental enrichment for caged cats in this study consisted of exposure to natural light, sound proofing (especially to exclude the noise of dogs barking), the provision of hiding and perching areas, and elevation of all cages above the level of the floor. No correlation between behavioral and hormonal data was determined. Based on urine cortisol concentrations, cats in enriched environments were found to be less stressed compared with those in nonenriched environments. In particular, exposure to dogs was associated with higher cortisol concentrations.

The lack of correlation of the behavioral and hormonal data in this study may have been due to the fact that misinterpretation of stress in cats is easy because signs often are inconspicuous, characterized primarily by inactivity.[18] Many of the cats in this study appeared relaxed based on their "laid out" posture and received low stress scores despite their elevated cortisol concentrations. Their relaxed posture may have been mistaken for feigned sleep, a behavior commonly associated with stress in wild felids. Feigned sleep is part of a passive defense syndrome that carnivores, particularly cats housed in zoos, show in response to stress, especially when adequate hiding places are not provided.[18] Findings of this study reinforce that activity depression and social withdrawal are indicators of stress in housed cats and human observers may not recognize stress readily.

RECOGNITION OF FELINE STRESS

Behavioral Needs of Cats

Stress recognition begins with an appreciation of the physical and behavioral needs of an animal. Indeed, the psychological and environmental needs of cats are distinct and unique from those of other species.[31-36] Most cats do not thrive in isolation. If allowed, cats develop highly structured, interactive social groups and seek the company of other cats frequently, thus the opportunity for social interactions is a basic behavioral need. Cats also require the ability to create different functional areas in their living environment for elimination, resting, and eating. Furthermore, they require the ability to regulate their body temperature by changing locations. They should be able to use horizontal and vertical space so that they can climb or jump to an elevated perch.

Cats require consistent routines or daily patterns of care, including consistent periods of light and darkness. Other important behavioral needs include the ability to find a hiding place, to sleep without being disturbed, and to be free of chronic harassment from human beings, other pets, or environmental stressors. Cats also require mental stimulation and the ability to play and exercise at will. Finally, cats need to scratch. Scratching is a normal behavior that conditions the claws, serves as a visual and scent marker, and is a means of stretching.

Behavioral Signs of Stress in Cats

Veterinarians are applied animal behaviorists and make use of posture, facial expression, vocalizations, and other behaviors to determine the "mental states" of their patients.[37] Manifestations of normal and abnormal behavior can indicate how successfully an animal is coping with its environment. In housed cats, feline behavioral expressions usually manifest via inhibited or withdrawal behavior, defensive behavior, disruptive behavior, and/or stereotypic behavior.[29,31] Inhibited or withdrawal behavior refers to activity depression or the absence of normal behaviors (e.g., grooming, eating, sleeping, eliminating, stretching, greeting people) (Figure 76-1). Defensive behavior involves

Figure 76-1. Feline stress manifests commonly with activity depression and withdrawal from normal activities such as grooming or exploration. **A,** A caged cat exhibits signs of acute stress, crouched and withdrawn in the back of a cage with dilated pupils. **B,** With chronic stress, caged cats commonly become inactive and depressed and may feign sleep.

Figure 76-2. A stressed cat exhibits a marked fear response when caged and confronted. Note the frozen stance, dilated pupils, and sideways, flattened ears. If approached more closely, the cat likely would respond with defensive aggression if an escape route were not available.

Figure 76-3. When caged in a novel environment, some cats respond by disrupting cage contents and creating a hiding place.

characteristic postural and/or vocal responses, and often is motivated by fear (Figure 76-2). Disruptive behavior involves destruction of cage contents and creation of a hiding place (Figure 76-3). Pacing, pawing, and circling are anxiety-related stereotypic behaviors (Figure 76-4).

As an illustration, consider the behavioral responses of a typical social domestic cat when caged in a novel environment. Most likely, the cat would respond initially with fear, and if threatened by the proximity of unfamiliar caretakers, defensive aggression may be displayed. If provided with a box for concealment, the cat probably would hide or otherwise slink against the back of the enclosure, behind the litter box, or disrupt the cage and hide under the paper. After a period of a few days, or possibly longer, the cat generally would adapt, becoming more active and engaging in greeting behavior by coming to the front of the cage and pawing or mewing as caretakers approach. If the cat remained confined over time without adequate periods of exercise, stimulation, or companionship, stress consequently would manifest with activity depression and withdrawal (e.g., lying in the litter box, failing to greet caretakers). Displays of stereotypic behavior (such as pacing)

Figure 76-4. Stressed cats may display anxiety-related stereotypic behaviors including pawing, pacing, or circling.

may occur; however, inhibited or withdrawal behavior would be more likely because it is much more common.

Behavioral signs of stress may be classified further as active communication signals or passive behaviors.[31] Signals of anxiety, fear, aggression, and submission may be subtle or obvious and include vocalization (growling, hissing), visual cues (facial expression, posturing of the body, ears, and tail), and scent marking (urine, feces, various glands of the skin).

Fear is manifested commonly by cats in novel environments. In general, cats would rather avoid than confront an anxiety-provoking or fear-provoking situation.[38] They are experts at escape and defense, but given the option they generally choose the former. Fearful cats may be overtly aggressive or passive and submissive. A submissive cat often is teetering on the edge. If no escape route is perceived and the challenge persists, the submissive cat may be forced into defensive aggression.[38] Furthermore, once provoked, cats may remain reactive for a prolonged time and may become more reactive if they are stimulated again during that period. Occasionally, fearful cats become completely immobile as though catatonic, rather than exhibiting aggression.

Passive signs of stress include inability to rest/sleep, feigned sleep, poor appetite, constant hiding, the absence of grooming, activity depression (decreased play and exploratory behavior), and social withdrawal.[12,28,31] These signs are exacerbated by high-density housing. Low social-order cats in such an environment exhibit decreased grooming, poor appetite, and silent estrus. Cats that are consistently fearful or anxious may hide, turn their back, huddle, and avert the gaze of other cats. Hiding is a normal and important coping behavior; however, when hiding is occurring with increased frequency or in response to stimuli that did not cause hiding previously, it should be recognized as a sign of stress.

In group settings, the complexity of the social structure cannot be overestimated. Within an established group, however, most social conflicts are not characterized by overt aggression. Instead, the main mode of conflict resolution is avoidance or deference.[31,38] Deference behaviors include looking away, lowering the ears slightly, turning the head away, and leaning backwards (Figure 76-5).[39] Large numbers of cats co-exist peacefully together using such strategies for avoidance.

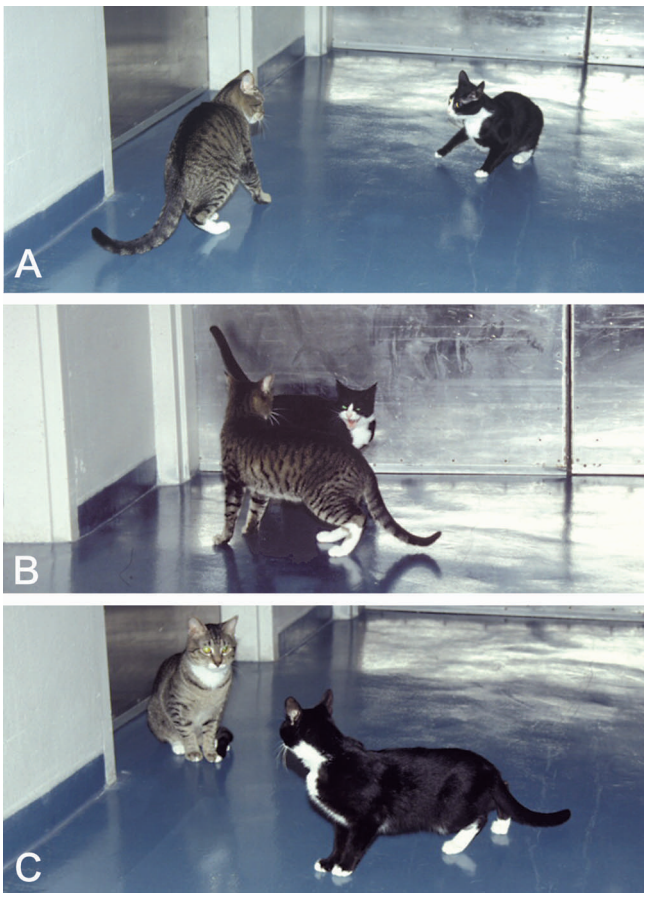


Figure 76-5. The major modes of conflict resolution for cats are deference and avoidance. **A,** An inquisitive cat *(left)* approaches a wary cat *(right)*. **B,** The wary cat exhibits an offensive warning signaling the approaching cat to stay away. **C,** Overt combat does not ensue; instead the cat on the left defers by simply sitting down a safe distance away.

Signs of social stress within groups of cats may manifest with overt aggression, increased spraying and marking, constant hiding, and stereotypic behaviors.[31] Lower-ranking cats may spend little time on the floor and remain isolated on single perches where they may even eliminate, whereas higher-ranking cats remain more mobile, controlling access to food, water, and litter resources.[36] High-density housing conditions frequently result in such abnormal behaviors, and also are associated with increases in transmission of infectious diseases and reproductive failure.[32]

The Role of Feline Personalities

Research has shown that most cats can be divided into one of two principal personality types: those who are outgoing, confident, and sociable, and those who are relatively timid and shy.[22] Temperament of the parents (particularly paternal effects) and early handling and socialization with both human beings and other cats are factors in the development of personality.[27,40,41] The personality of a cat has been shown to affect adaptation to various housing.[19,42] Cats with bold, friendly temperaments tend to cope and adapt more readily than shy, timid cats.

Other personality traits also may influence housing and adaptation, particularly in a group setting.[31,36,43] "Assertive" or "bully" cats are those unwilling to allow others to live with them unmolested. They may threaten other cats in a group setting to control access to food, litter, perches, or the attention of human caregivers. Aggression does not have to be overt: in fact, aggression most often is covert and involves stares and postures. The assertive cat challenges those in higher social positions constantly and bullies those in subordinate positions. Such aggression usually is not directed towards human beings. In fact, this cat may be particularly interactive with caretakers. To maintain harmony, removing cats of this personality type from the colony often is necessary. Reassignment is possible but may prove difficult, which necessitates single housing.

Cats of the shy, timid personality type may not interact successfully with more dominant members of a group or may fall victim to a bully, resulting in withdrawal behavior and increased hiding. Placement of such cats in smaller groups or with juvenile cats where they can develop affiliative relationships generally is rewarding.[31,36]

MANAGEMENT OF FELINE STRESS

Implications

Cats may be hospitalized for illness or elective procedures; admitted to animal shelters, boarding, or quarantine facilities; or maintained in research laboratories, private homes, or catteries. The provision of proper enriched housing improves cat welfare regardless of the location or length of stay. In addition to improvement of the emotional and behavioral well-being of cats, better housing has a variety of other implications. For example, in a hospital setting, when special feline needs are overlooked, the resulting stress can result in complications (such as anorexia) that will delay recovery. Veterinarians must learn to recognize the importance of stress management as an essential component of a comprehensive medical plan for their patients, regardless of the presenting illness or problem. Common sense dictates that separating feline wards from areas with barking dogs is essential for proper management of stress, but this is neglected frequently in veterinary hospitals.

The implications for properly enriched housing of cats in animal shelters also are great. More cats than dogs are euthanized in shelters in the United States, and millions of healthy homeless cats die each year.[44,45] Less than 10 to 15 per cent of owned cats are obtained from shelters; therefore, increasing adoptions represents one important strategy for shelters to decrease euthanasia.[46] In animal shelters, enriched housing may improve cat welfare during shelter stays and may increase adoptions by attracting potential owners and therefore save the lives of more cats. Viewing cats in traditional cage environments may represent a negative or troubling experience for potential adopters, who elect to avoid these environments. Increasingly, private "no-kill" shelters provide attractive venues for pet adoptions, while affording pets long-term stays. Opportunities for long-term stays in animal shelters make the provision of enriched housing even more important and establish a model for future sheltering. Finally, improved housing in laboratory settings enhances cat welfare and also yields better subjects for research and more reliable data, and affects public perceptions positively.[17]

Housing Design

Proper housing meets the behavioral needs of the animals and thereby minimizes stress. Careful planning of facility design,

Figure 76-6. Installation of multiple runs in a room is an economical use of floor space and allows cats to be housed comfortably in small compatible groups.

Figure 76-7. In colony room housing, construction of a chain link foyer at the entrance prevents cats from escaping through the room door when it is opened.

Figure 76-8. Particular attention to the provision of solid surface ceilings in housing enclosures is essential to prevent the escape of crafty cats into the rafters. Once in the ceiling, cats may be difficult to recover and may become injured and/or cause substantial damage to facilities.

adoption of strict management protocols and preventive health care programs, thorough training and supervision of personnel, and oversight by a knowledgeable professional are keys to success.[17] Provision of group housing is important for animal welfare. Individual housing of cats should be avoided unless particular objectives dictate the use of single-cage housing, or if caging is needed for short periods to permit collection of specimens, treatment, observation, isolation, quarantine, cleaning of group enclosures, or introduction of new colony members.

The design of long-term housing should provide space that is mentally and physically stimulating, easily cleaned, well-ventilated, safe for cats and caregivers, and aesthetically pleasing. A variety of indoor colony designs are suitable for cats. Installation of multiple runs within a room is the most economical use of floor space in many cases (Figure 76-6). When a free-ranging room arrangement is used, a fence "foyer" may be constructed adjacent to the door inside the room to allow personnel entry into the room without giving any opportunity for cats to escape (Figure 76-7). Regardless of the arrangement used, wall, floor, and ceiling surfaces must be sanitized easily. Sanitation requires durable, impervious surfaces; sealed flooring; plumbing with drains that can handle waste, food, and hair; and solid surface ceilings. Solid surface ceilings also are important to prevent escape of cats (clever cats may push out ceiling tiles and enter the rafters) (Figure 76-8).

In some situations, outdoor enclosures also may be suitable for cats. Benefits include ample exposure to natural light, excellent ventilation, and mental stimulation. Galvanized wire chain link panels with 1-inch mesh (including a top panel) or specially designed fencing for cat enclosures (Benner's Friendly Fence, http://www.purrfectfriendlyfence.com) may be used.

Figure 76-9. If cats must be caged, they should be housed in compatible pairs to ensure social companionship whenever possible. Resting boards and hiding places should be provided and serve to reduce stress. The old saying that two cats are better than one usually is true.

In most instances, cats benefit from being housed together as long as they are provided with sufficient space, easy access to feeding and elimination areas, and an adequate number of hiding and resting places. Housing cats in small groups of up to four to eight individuals is ideal in most settings, because monitoring individual cats in smaller groups generally is easier and space limitations may prevent larger groupings. Even if space availability permits larger groupings, these generally are not recommended, especially in animal shelters, because introduction of infectious disease is common even in the most well managed shelter. If cat group numbers are small, disease exposure is limited, which facilitates control of outbreaks (see Chapter 77). In a closed-colony laboratory setting, larger groups of 15 to 25 cats may be established successfully; however, groupings of more than 30 individuals are not recommended.[32,47]

At a minimum, cats should be housed in compatible pairs (Figure 76-9). In breeding colonies or catteries, cats can be housed in small groups of the same sex when not breeding, or in harems (consisting of a few queens with a tomcat) when breeding.[17] Compatible pregnant queens should be together because they usually share nursing and neonatal care (Figure 76-10). Pregnant queens should be housed together before delivery, because some queens may not accept the addition of a new queen readily once she has delivered her kittens.[17]

In animal shelters, cats should be spayed or neutered before group housing whenever possible, after which compatible males and females may be housed together. At a minimum, tomcats should be neutered to prevent inter-male aggression, urine spraying, and breeding.[48] Spay/neuter is recommended before puberty (or before 5 months of age) and before adoption (as early as 8 weeks of age) to ensure well-being, compliance, and population control.

Groupings should be established based on age as well as reproductive status. To ensure social companionship and proper social and emotional development, kittens should be housed with their mothers until weaned or up to 12 weeks of age. The mother-kitten relationship is important for normal development, and early-weaned or orphan kittens may fail to develop normal social skills and/or have maladaptive responses to stress.[49] Most queens accept the kittens of another; therefore young orphan or singleton kittens should be housed with other lactating queens and/or kittens of similar age or size.

Beyond 12 weeks of age, kittens generally have strong immunity and can be housed with other juveniles. Juveniles generally exhibit healthy activity and play behavior with conspecifics up to 9 to 12 months of age. Adult cats should be kept separate from juvenile cats, and aging or old cats separate from other age groups. In animal shelters, compatible cats that enter the shelter together should be housed together either alone or with other cats whenever possible.

In established groups of cats, introduction or removal of individuals requires a period of adjustment, which usually is stressful, and may induce fighting and/or disrupt breeding.[17] These signs usually subside once a new social hierarchy and territorial limits (usually favored resting places) are established. In multiple-run housing within a single room, rearrangement of run groups or even relocation of a stable group within the room may induce imbalance of the social order and anxiety. Therefore every effort should be made to minimize reorganization of groups once they are established. In the case of animal shelters, where population interchange is high, it is not feasible generally to maintain consistent groupings of cats because new cats must be introduced frequently.

Tremendous individual variation exists among cats in the context of social relations with other cats.[31,39,50] Although introduction of some cats seems effortless and uneventful, introduction of others results in considerable stress for the new cat and the entire group. In fact, bringing a new cat into an established colony is analogous to having a stranger move into your home and share your personal bath and living space.[39] For this reason, introduction of new cats should be done slowly, under supervision. To accomplish this, a new cat should be kept in a separate cage within the group enclosure equipped with food, water, litter, and a hiding box. Usually within a few days or 1 to 2 weeks, the new cat can be transferred smoothly into the enclosure with little overt aggression resulting. The use of synthetic analogues of naturally occurring feline facial pheromones (Feliway, Veterinary Product Laboratories, Phoenix, AZ) may facilitate harmonious introduction of a strange cat into an established group.[47] Well-socialized kittens and juvenile cats frequently adapt readily to group accommodations, and prolonged introductions may not be necessary unless they are shy or undersocialized. Cats that show persistent incompatibility with conspecifics (even when pair-housed with a smaller/younger cat) should be housed singly. Shy or assertive cats may show their "best side" in individual housing, which facilitates adoption.

Behavior problems may occur even in modestly populated, carefully introduced, environmentally enriched colonies. Manipulating the social environment by regrouping cats may help to resolve these problems. Many cats are incompatible with one another either as housemates or as sexual partners. If only one or two cats are responsible for social destabilization of a colony, they can be removed and reassigned to another colony. Often it is the social grouping, not the individual, that is the problem.

In time, a careful observer sees that cats usually divide themselves into amicable groups. Observers should note feline personality types and watch for behavioral signs of stress in addition to affiliative behaviors. The best colony environments are those that produce the most "normal" behaviors, including

Figure 76-10. In breeding colonies, compatible queens may be housed together before and after delivery. **A,** Two queens share the care of their litters of kittens. Most queens readily accept and care for the kittens of other queens. **B,** Perches should be provided to allow mother cats a period of rest away from their young.

grooming, sleeping, playing, stretching, allorubbing, exploring, and displays of estrus. Colonies should be monitored to ensure that all colony members are content in the social environment.

The success of adaptation of cats to novel environments depends on both the quality of the environment and the adaptive capacity of the cat. Although most cats adapt to new environments over time, some never adjust and remain stressed indefinitely, which ultimately results in decline of physical and emotional health. Novel environments tend to be especially stressful for poorly socialized cats and for old cats. Housing of feral cats should be avoided whenever possible. Old cats in animal shelters generally benefit from placement in foster care, and owned old cats from outpatient or in-home care rather than hospitalization or boarding.

The high turnover rate of cats in shelter settings contributes substantially to feline stress levels.[51] When group-housing shelter cats, close attention to social groupings, population density, environmental enrichment, and monitoring is essential to promote cat welfare rather than exacerbating feline stress. I recommend that shelters maintain a variety of housing styles to meet the wide array of behavioral needs of individual cats whenever possible.

Size of Enclosures

Enclosures for cats should be large enough to allow them to stretch, groom, and exercise, while maintaining separate functional spaces (at least 0.5 m apart) for sleeping, eating, and elimination. Adequate space allows individuals to enjoy normal activities while coexisting peacefully with conspecifics, either through affiliative relationships, easy avoidance, or both. Minimum floor space requirements should be based on the social spatial needs of animals and not on body weight.[47] Table 76-2 shows the current recommendations for cat enclosures in the United States and Europe. In my opinion, only the proposed revisions by the Council of Europe Process are adequate for long-term housing of cats (e.g., confinement of greater than 2 to 4 weeks). These recommendations are for 1.5 m^2 of floor area with 2 m height, combined with the provision of shelves, a box-style bed, and vertical scratching objects. The vertical dimension must be at least 1.5 m high so that elevated resting surfaces can be installed well above ground level; however, walk-in enclosures (2 m) are ideal so that caretakers can enter easily and interact closely with the cats.[47]

Enclosure sizes and cat numbers used or recommended by a variety of other organizations or authors may be found in Tables 76-3 and 76-4. Doubling the size of an enclosure does not necessarily allow a twofold increase in the number of cats that can be housed properly within. For singly housed cats, one organization uses two-roomed lodges with glass walls, equipped with small openings to allow olfactory and visual communication with other cats, plus a garden view, heated beds, and rope toys for scratching and play.[52-54] In addition, cats receive 20-minute daily sessions of one-on-one attention from a human caregiver.

Preventive Medicine Considerations

In a group setting, proper medical care, quarantine procedures, and individual identification of cats prior to introduction to a group are critically important. Identification in the form of a tag, microchip, ear band, or tattoo is essential for preventive health care and ongoing surveillance of individuals, particularly in group settings (Figure 76-11). Once the cat is housed with the group, monitoring of individuals may be difficult; therefore cats should have their weights recorded weekly, and cats that appear sick for any reason should be removed and housed individually for observation and treatment. Likewise, elimination behavior should be monitored closely in the colony. Inappropriate elimination may be an indicator of social stress and/or a medical issue. If the provision of ample, regularly cleaned litterboxes does not resolve the problem, vigilance to determine the culprit is necessary.

Table 76-2 | **Recommended Space for Housing Cats**

	FLOOR AREA PER CAT		HEIGHT	
	m^2	ft^2	m	in
U.S. NATIONAL ACADEMY OF SCIENCES[67]*				
Cats <4 kg	0.27	3.0	0.61	24
Cats >4 kg	0.36	≥4.0	0.61	24
COUNCIL OF EUROPE PROCESS: CURRENT RECOMMENDATIONS[68]†				
Cats 0.5-1 kg	0.2	2.2	0.5	19.7
Cats 1-3 kg	0.3	3.3	0.5	19.7
Cats 3-4 kg	0.4	4.4	0.5	19.7
Cats 4-5 kg	0.6	6.6	0.5	19.7
COUNCIL OF EUROPE PROCESS: PROPOSED REVISED RECOMMENDATIONS[69]‡				
One adult cat	1.5	16.7	2	78.7
Each additional adult in same enclosure	0.75	8.3	—	—

*Raised resting perch required.
†Shelves, scratching objects, and daily exercise required.
‡Shelves, box-style bed, and vertical scratching objects required.

Animal Care Staff, Socialization, and Handling

Animal care staff must enjoy working with cats and be willing to interact with them to assure socialization and tractability. Cats become entrained to daily routines and generally respond strongly to their human caregivers.[6] Whenever possible, caregivers should be assigned to care for the same cats on a regular basis so that they become aware of the personality of each individual cat, which is necessary for detection of health problems, incompatibilities between cats, and in the case of breeding colonies, estrous cycling. This also is important because not all cats enjoy human companionship and are more likely to be stressed by the presence of different caretakers, rather than becoming familiar and more at ease with one. In general, regular daily contact and socialization are essential to ensure that cats are docile, easy to work with, and have no fear of human beings. Caretakers should schedule time each day to interact with "their" cats outside of the activities of feeding and cleaning. Some cats may prefer to be petted and handled, whereas others prefer to interact via a toy. Daily social contact and exercise sessions with human beings are especially important for individually caged cats.

Social companionship may be associated with highly pleasurable feelings, which act as a strong motivator or reward for social interaction, of which the neurological basis involves activation of brain opioids and other neuropeptides known to be associated with pleasurable feelings. Social contact, however, is not invariably pleasant for all cats. Personality, socialization, previous experience, and familiarity contribute to whether or not social interactions are perceived as pleasurable, stressful, or somewhere in between.[21,55]

The implications of such findings provide a scientific rationale for practice of compassionate care and management of animals. In the context of a veterinary hospital, human contact can be beneficial during all stages of illness and healing. Hospital personnel can offer gentle contact, but research suggests the best approach is contact with familiar people. Thus frequent visitation of pets in hospitals, quarantine facilities, and boarding catteries should be encouraged strongly. Goals also should include nurse-patient or caregiver-cat bonding, and continuity of care throughout the stay. Whenever possible and feasible, pet owners should be encouraged to be present for medical procedures just as in human pediatric medicine, where parents are encouraged to maintain contact with their infants during these events. Research indicates that gentle human contact can attenuate the adverse effects of unpleasant stimuli, eliminate fear responses, and alleviate signs of pain in animals, which supports

Table 76-3 | **Selected Space Recommendations for Cat Housing**

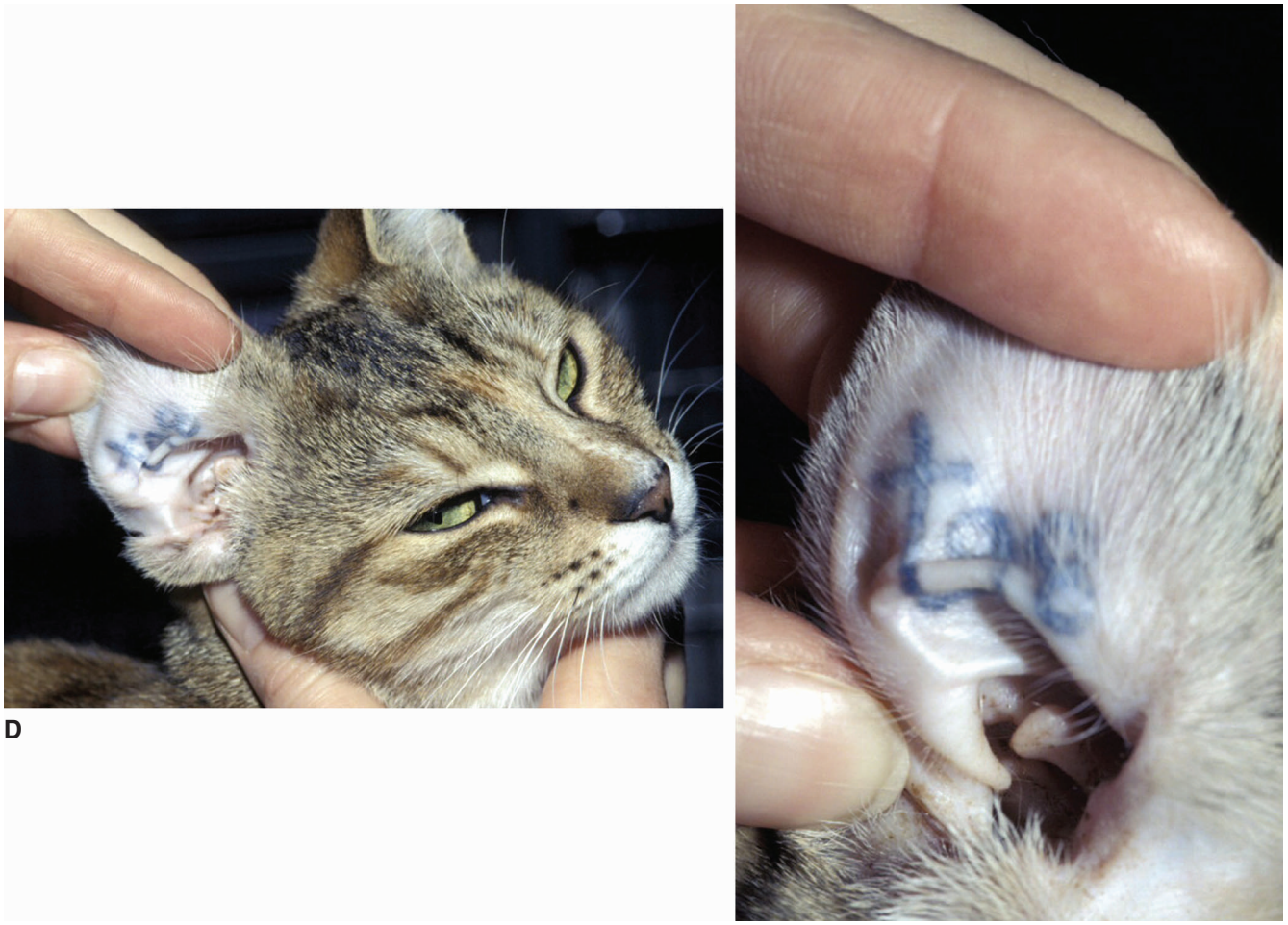
		FLOOR AREA PER CAT		HEIGHT	
		m^2	f^2	m	in
Waltham Center for Pet Nutrition[32]	Group-housed cats	1.0	11.1	2 m	78.7
	Caged cats	0.75	8.3	0.8 m	31.5
Best Friends Animal Society[70]	Indoor housed cats	0.93	10		
	Outdoor runs	1.4	15		
Kessler and Turner[20]	Group-housed cats	1.7	18.8	1.8	70.9
	Caged cats	Not specified			

A

B

C

Figure 76-11. Individual identification is essential for cats, particularly when group-housed. Methods of identification include collars with tags, microchips, ear bands, and tattoos. **A,** Collar and tag identification. Breakaway or stretchable safety collars are recommended. **B,** Microchip identification: Small (12 × 2 mm) microchips can be implanted easily in most cats without sedation using a needle. Cats may be scanned for reliable permanent identification. **C,** Ear tag or band. Small ear bands are manufactured for wing banding of birds and are ideal for identification of young kittens in a laboratory setting.



D

Figure 76-11.—cont'd. D, Permanent tattoo on the inner pinna of the ear of a cat. The medial aspect of the thigh and the groin area are other common sites for tattoo placement; however, growth of hair makes reading difficult. Heavy sedation with appropriate analgesia is required for tattoo placement.

Table 76-4 | **Group-Housing Recommendations from Selected Organizations**

ORGANIZATION	MAXIMUM NUMBER OF CATS IN ROOM	ROOM SIZE (IN FEET)
San Francisco Society for the Prevention of Cruelty to Animals, CA[71]	2 6	4 × 6 12 × 18
Humane Society at Lolly Pop Farm, Fairport, NJ[71]	8	6 × 12
Humane Society of the United States[71]	10	10 × 15
New Hampshire Society for the Prevention of Cruelty to Animals[71]	10	13 × 16
Good Mews Cat Shelter, Atlanta, GA[72]	2 15*	5 × 7 10 × 14
Auburn University[36]	8	12 × 18

*Kitten room (juveniles 3 to 9 months of age only).

the value of such an approach in veterinary medicine and animal care in general. The presence and caring touch of the pet owner or familiar caregiver may be an important benefit during many procedures that involve pain, fear, or other emotional distress.[55]

In animal shelters, socialization programs often are needed for feral kittens and shy adult cats. A study of 70 feral kittens demonstrated they can become good pets with bold and friendly temperaments, and that handling before 7 to 8 weeks of age improved socialization success.[56] An excellent source of information pertaining to taming feral kittens may be found at the web site of the Feral Cat Coalition, San Diego, CA (http://www.feralcat.com/taming.html). Shelter cats with timid or shy personalities also may benefit from one-on-one interaction with a human caregiver; however, the caregiver should be a consistent person to reduce stress on the cat and facilitate adaptation. The use of massage techniques to aid in relaxing or calming shy cats has been described.[57]

Handling and restraint of cats of varying ages, personality types, social experiences, and stress levels require skill, knowledge of normal feline behavior and signaling, and finesse. Most cats respond best to gentle restraint and detest being "over-restrained." To minimize stress and "fight-or-flight" behaviors, cats must perceive they are maintaining some control over their situation during restraint and handling. Allowing cats to "hide" their faces under a towel or in the nook of the handler's arm, providing time for them to acclimate to new surroundings before handling, avoiding escapes and the need to recapture, and using transport carriers are helpful methods of reducing stress successfully when handling cats. If fight-or-flight responses appear impending, easing restraint may allow cats to continue to cope rather than to attempt escape or defense. In

some cases, chemical restraint is necessary to protect the handler, to prevent severe stress, and to promote cat welfare.

Environmental Enrichment

Studies indicate consistently that mental stimulation is emotionally rewarding to animals, and that novel stimuli are associated with positive feelings.[21] Stimulus-deficient environments should be avoided. Likewise, a sense of control over conditions is one of the most critical needs for mental health and well-being in animals. Certainly this holds true for cats. They need variety and choice, and individual cats possess different preferences for environmental conditions, levels of activity, and social interactions with other cats and human beings. The best environmental enrichment provides for all of these choices.

Above a critical minimum, the "quality" of space is more important than the quantity.[58] A variety of elevated resting perches and hiding boxes should be provided, to increase the size and complexity of the living space and to separate it into different functional areas and allow a variety of behavioral choices (Figures 76-12 through 76-15). The physical environ-

A

B

Figure 76-12. Traditional cage housing can be enhanced markedly by the provision of proper resting perches and hiding places, dividing the space into different functional living areas. Placement of a Hide and Perch Box (British Columbia Society for the Prevention of Cruelty to Animals) in a traditional cat cage improves the quality of the space and the welfare of the cat. Such living arrangements should be utilized in all novel settings where cats are housed whenever possible.

Figure 76-13. In a group setting, a variety of resting perches helps to create different functional living spaces and behavioral options for cats. Note the separation of food and water bowls from litterboxes.

Figure 76-14. Installation of shelving in a colony room provides ample opportunities for exercise, hiding, escape, and perching. The arrangement is aesthetically pleasing, and may facilitate interaction of potential adopters with cats in animal shelters.

Figure 76-15. A variety of commercially available condo-style housing units is available for cats. They separate functional living areas, provide improved opportunities for exercise and exploration, and generally represent an improvement over traditional cage housing.

Figure 76-16. Installation of a free-standing tower in this colony room allows cats to use horizontal and vertical space and functionally reduce overcrowding.

ment should include opportunities for hiding, playing, scratching, climbing, resting, feeding, and eliminating.

A minimum of one litterbox per two cats and one food and water bowl per three cats should be provided and arranged in different locations of the room. Food and water should be separated from litter by at least 0.5 m. The number of resting boards and perches should exceed the number of cats and should be arranged in as many locations within the enclosure as possible, from the floor to near the ceiling. If not enough comfortable, desirable resting places exist, cats use their litter trays for this purpose. In breeding colonies, nursing queens must have perches so that they may have rest periods away from their young (see Figure 76-10). In larger colony rooms, installation of freestanding towers provides additional living and activity space and contributes to reducing overcrowding functionally (Figure 76-16). Whenever possible, comfortable bedding (either disposable or that can be laundered easily) should be provided. Cats demonstrate preferences for resting on soft surfaces and they experience longer periods of normal deep sleep with soft bedding.[59]

Resting perches in view of windows or other pleasant areas of the facility are especially desirable. The provision of bird-feeders, gardens, or other interesting stimuli in the external environment can enhance the internal environment of the colony.[60] This is especially important for cats housed singly because, if housed in view of other cats, they will be less isolated and can participate in visual and olfactory communication with other cats.

Full spectrum and/or natural lighting is ideal, and regular cycles of light and dark should be maintained. In breeding colonies, light schedules of 12 (hours) light:12 dark or 14 light:10 dark are optimal to ensure reproductive cycling.[17] Loud noises and intense or aversive stimuli (such as dogs) should be avoided. A radio playing soft, low music in the room provides a welcome distraction and important source of stimulation. In addition, it may help habituate cats to human voices and prevent them from being startled by loud noises. Most caretakers also enjoy listening to the radio, and happy caretakers create a relaxed environment. The environmental temperature should be kept comfortable and constant, and living quarters should be well ventilated, without drafts. By changing location within the colony, from the cooler surface of the floor to a sunny window, cats can choose the environmental condition they prefer.

Provision of scratching boards is especially important. Some cats tend to pick with their claws, whereas others rake in long strokes. Ideally, a variety of sturdy surfaces, horizontal and vertical, should be provided for scratching. Sisal rope, carpet squares, and corrugated cardboard are useful.

Play items that stimulate activity such as plastic balls, rings, hanging ropes, spring mounted toys, plastic wands, and catnip toys also should be provided but must be sanitizable or disposable. Empty cardboard boxes and paper bags are inexpensive, disposable, and stimulate exploration and play behavior, in addition to scratching. Cats tend to be most stimulated by active toys including wiggling ropes, wands with feathers, kitty

Figure 76-17. Enrichment does not have to be complex or expensive. Cats become accustomed to regular daily activity patterns, which often are enriching and rewarding. Pictured here, laboratory cats eagerly await the daily routine of the caregiver turning the faucet on for them to drink.

fishing poles, and toys that can be slid or rolled to chase. Many cats enjoy chasing the beams of laser pointers, small flashlights, or suspended rotating disco balls. Varied toys should be substituted regularly to ensure continued interest.[61,62]

Novel presentation of food to stimulate "pseudopredatory activity" has been a source of enrichment for several felid species.[63] Dry cat food can be hidden in commercially available food puzzle toys, or in cardboard boxes, tubes, or rolling toys with holes such that the cat has to work to extract pieces of food. Many cats like to chew grass, and containers of cat grass or fresh catnip can be introduced for brief periods to stimulate activity. Other novel and enriching stimuli include cat-proof aquariums with fish, water fountains, and videotapes especially designed for cats[64] (Figures 76-17 and 76-18). Obedience training using clickers with food or play rewards can provide additional stimulation and activity.[65]

Finally, use of a commercially available feline facial pheromone spray (Feliway, Veterinary Product Laboratories, Phoenix, AZ) may provide environmental enrichment by reducing stress. Facial pheromones are deposited when cats rub on prominent objects or allorub other cats when they feel safe and at ease. In a study of hospitalized cats, spraying Feliway in cages before admission resulted in increased food intake and grooming behavior of cats.[66]

CONCLUSION

Proper housing meets the behavioral needs of cats and results in frequent displays of normal feline behaviors. Close attention to their unique needs and stress responses has profound implications for improvement of their welfare. Even a few small changes have the potential to affect their emotional health profoundly, which in turn may result in such positive benefits as

Figure 76-18. A shelter cat watches a specially produced feline video. Provision of adequate mental stimulation is essential for cat welfare.

more rapid recovery from disease, prevention of disease altogether, and enhanced detection of early subtle signs of illness that otherwise might be attributed to housing stress. In an age of technological advances in animal care, the profound comfort and scientifically proven benefits of simple things such as a soft bed, a hiding spot, and a place to perch, rub, or scratch must not be forgotten.

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Chapter 77

Controlling Feline Respiratory Disease in Animal Shelters

Janet M. Scarlett

Numerous papers have been written about the control of upper respiratory tract disease (URTD) in cats.[1-8] Despite adopting recommended measures, many animal shelters continue to experience a high endemic level of URTD and periodic outbreaks of respiratory disease. The degree to which preventive measures "work" depends on a wide range of factors: environmental, management, agent-related, and host-related. Because the incidence of URTD is affected by multiple factors and these factors can vary among shelters, the importance of developing shelter-specific URTD control programs cannot be overemphasized. Veterinarians should help shelters to formulate specific URTD-related goals and strategies tailored to their facilities, and after implementation, to evaluate the effectiveness of their programs.[9] If the goals are not achieved, then strategies need to be reevaluated and modified, and the process repeated.

Veterinarians familiar with vaccination, diagnosis, and treatment of URTD in client-owned cats (which usually come from one-cat to three-cat households) often are unprepared for the challenges these same agents present in shelters. Small animal veterinarians generally are unfamiliar with the "herd health," goal-driven, systematic process that is required to minimize disease occurrence successfully in shelter populations.

Previous manuscripts have reviewed the epidemiology of the most common agents causing URTD in cats.[10-12] The nature of these agents makes their eradication impossible and their control challenging, even under the best of circumstances. The objectives of this chapter are to discuss URTD control strategies and to suggest a systematic approach to minimize URTD incidence in animal shelters. For the purpose of this chapter, an animal shelter is defined as a population of homeless cats housed together in a facility.

DISEASE CONTROL AND PREVENTION

Feline herpesvirus-1 (FHV-1, formerly feline rhinotracheitis virus [FVR]) and feline calicivirus (FCV) are the most common causes of URTD in cats.[1,10,11] Other agents contributing significantly to disease include *Bordetella bronchiseptica*, *Chlamydophila felis,* and *Mycoplasma* spp.[11] The role of calicivirus and herpesvirus as primary respiratory pathogens is well established.[12,13] *Chlamydophila felis* (formerly *Chlamydia psittaci*) once was believed to cause a broad spectrum of respiratory signs but is now recognized primarily as a cause of conjunctivitis in cats.[14-16] *B. bronchiseptica* acts as a primary pathogen under laboratory conditions,[17,18] and recovery of only this organism from cats with respiratory disease in the field suggests that the organism also can act as a primary pathogen there.[19]

Mycoplasma spp. are normal inhabitants of the upper respiratory tract of cats.[20,21] They are not found in the lungs of healthy cats but have been recovered from cats with lower respiratory tract disease.[22] They are believed to be opportunistic invaders primarily, but in some cases of lower respiratory tract disease they may act as primary pathogens.[23]

Although the principles of preventive medicine are known, what is unclear is how they apply to all possible mixtures of environmental, management, agent, and host factors associated with feline URTD in shelters. To provide structure to the following discussion, strategies for disease control and prevention

have been divided into six sections (somewhat arbitrarily) on the basis of their effect on disease control. Some categories overlap.

UPPER RESPIRATORY TRACT DISEASE SURVEILLANCE: ESTABLISH A SURVEILLANCE SYSTEM

Assessing the magnitude of the current URTD disease burden in a shelter and the subgroups at highest risk, and ultimately evaluating the effectiveness of control efforts, requires reliable information regarding URTD incidence.[9] Therefore, in development (or reassessment) of a shelter's URTD control program, an important early step is the creation of a URTD surveillance system.

The surveillance system need not be complex or highly sophisticated. In fact, starting simple can help ensure that staff and volunteers understand the procedures and comply easily. Regardless of its sophistication, four elements are essential: prompt and accurate disease recognition, willingness to report, a data capture and analysis component, and a means to communicate the results. Staff and volunteers should be trained to recognize and promptly report cats displaying signs of URTD, including any unusual occurrence of signs or changes in mortality that may be attributable to a new strain of calicivirus (see Chapter 1). Unfortunately, although people readily learn to identify most cats with respiratory signs, the challenge is to motivate them to report. This reluctance often is associated with the fear that reported cats will be marked for euthanasia or spend days in isolation. Staff and volunteers must understand that leaving cats that are actively spreading a highly contagious agent increases the agent load in adoption areas, contaminates fomites, including people handling them, and thereby dooms healthy cats to infection.

Surveillance means more than just early detection of sick cats, however. It also involves the regular, systematic collection, recording, and analysis of data regarding the frequency (i.e., incidence) of URTD over time. The recording should be straightforward, which leads to easy analysis and reporting of results. This may involve a commercially available shelter-specific software program but could involve a spreadsheet or even a handwritten tally system.[9] Surveillance enables shelters to assess the incidence of URTD, set realistic goals, develop targeted strategies, and monitor the effectiveness (or lack thereof) of their URTD-control programs, which leads to better overall management of URTD. Reporting declining URTD incidence to staff and volunteers can encourage continued commitment to the program. Discovering increasing or unchanging disease levels can lead to adoption of alternative measures and serve as the basis for seeking more resources for URTD control or making other relevant changes.

EDUCATION AND MOTIVATION: BUILD A URTD-CONTROL TEAM

Of course, an URTD-control program will not work if staff, volunteers, and the public are not educated and motivated to participate. Education and motivation may be the *most* important means to minimize URTD in animal shelters. Although veterinarians are well aware of the epidemiology of URTD agents, some staff (even senior staff) and volunteers may not be. Periodic training sessions for new and continuing employees educate and build a team effort to reduce URTD. Staff members should be involved also in goal setting so that they have a vested interest in achieving the goals. Once goals have been set, staff and volunteers should be encouraged and motivated daily to maintain commitment to disease reduction.

MINIMIZE AGENT CONCENTRATION IN THE ENVIRONMENT

Cat Density: Avoid Overcrowding

Housing more cats in an area than can be cared for appropriately is a common occurrence in shelters. In an effort to help as many cats as possible, shelters often overcrowd, which puts cats in residence at higher risk of URTD and of more severe disease (as compared with cats with lower-density housing). This almost always comes at the expense of the quality of care provided by the shelter.[9] Crowding increases stress and the amount of agent in the environment and makes effective cleaning and disinfecting and adherence to handling protocols more difficult. More lives likely can be saved by minimizing the incidence of URTD and by displaying the cats in clean, uncluttered facilities, than by attempting to shelter as many cats as possible.

Optimal density recommendations for shelters based on scientific studies do not exist. Recommendations based on federal guidelines for research cats are minimal, and the goals of research facilities differ from those of shelters. As a rule of thumb, if recurrent outbreaks or high rates of URTD occur despite good control protocols, the housing probably is too dense.

Hygiene: Clean and Disinfect Thoroughly and Frequently

In the design and implementation of a URTD-control program, the importance of a shelter's cleaning, sanitizing, and disinfecting (CSD) protocol is paramount.[25-28] In evaluation of CSD protocols, fomite transmission is one of the most (if not the most) important means of transmission of respiratory agents in most shelters.

The first step in a good CSD protocol is education of staff. They must understand the importance of a rigorous protocol, procedures to achieve that protocol, and common pitfalls. Numerous sources outline protocols in detail, and the reader is encouraged to consult them.[29,30] Comments regarding pitfalls, however, and emphasis on components particularly important in URTD control are discussed below.

Cats always must be removed from cages before cleaning, and cages always must be dry before return of the cat(s). Staff members must understand that fomites include cages, cage bars, food and water dishes, litterboxes, sleeping mats, toys, and cat trees. Therefore these sources first must be cleaned thoroughly, and cleaning must precede disinfection (because common disinfectants are unable to penetrate and kill organisms in organic debris). Most disinfectants also are inactivated by organic matter.[26-28] This means that all surfaces in a cage (walls, floor, ceiling, cage bars, and shelves) must be cleaned carefully. Cage doors with bars or mesh are common sources of wet or dried mucous secretions that can harbor viruses or bacteria. These should be given extra attention in cleaning and disinfection. Failing to remove pathogens effectively puts subsequent cats at risk of infection.

Placement of cats during cage cleaning varies.[26] Disposable cat carriers, specific to each cat and sent home with the adopter, probably are optimal (if resources allow). The relative efficacy of the various approaches to housing during cleaning in prevention of new infections is not known. Cats should not be allowed to wander the floors, including in the isolation room, because this almost assuredly spreads disease to subsequent cats.

Often overlooked as fomites are people.[25] Staff members, volunteers, and the public handle cats while transferring them between cages, examining for disease, socializing, or deciding on adoption. Secretions from infected cats can be transmitted from cat-to-cat during these interactions. Wearing aprons that can be cleaned between cats and having sinks or, preferably hand sanitizers,[31] and *requiring* people to use them can reduce URTD transmission.

Staff members who clean isolation areas should not clean areas where healthy cats are housed. If this is not possible, then areas housing healthy cats and their cages should be cleaned and disinfected before quarantine areas and these before isolation areas. Similarly, kitten areas should be cleaned before areas with more mature cats. Each housing area should have its own equipment and supplies that are restricted to that area. Hot and cold water in each cleaning area is ideal. If staff must travel between areas after handling sick or high-risk cats or potentially contaminated equipment, hands and washable aprons should be washed thoroughly. If washable aprons are not available, then separate smocks for the isolation and quarantine rooms should be used in those areas only. Attention should be directed to regular cleaning of meet-and-greet areas, because animals may move in and out of these rooms frequently on busy adoption days.

Products

The two most common types of disinfectants used in shelters are quaternary ammonium products (e.g., Roccol, A-33) and sodium hypochlorite (i.e., bleach).[26] Quaternary ammonium products usually are effective against enveloped viruses (e.g., herpesviruses) and bacteria,[25,32,33] are less corrosive than bleach,[28] and are good at minimizing odors in shelters. Their effectiveness is reduced by the presence of soap and hard water and low pH[27,28] and they do not all perform equally. They do not inactivate calicivirus completely, despite claims to the contrary.[33] For this reason, sodium hypochlorite (i.e., bleach) or one of the newer products (described below) should be included in shelter disinfection protocols. Sodium hypochlorite at a 1:32 dilution is effective against calicivirus.[34] If bleach is used, solutions must be prepared the day of use, diluted to an appropriate concentration: 1:32 for general disinfection (½ cup per gallon of water), stored in a non-clear container, allowed to remain on the surface for at least 10 minutes, and rinsed away before cats are reintroduced into their cages.[25-27] Because of the corrosive properties of sodium hypochlorite, a rotation of products may be practiced (e.g., quaternary ammonium products one day, bleach the next or other combinations). Staff members must understand that because a 1:32 dilution is recommended, a lower dilution (more concentrated solution) is *not* necessarily better. Lower dilutions, although sometimes employed in the face of outbreaks (e.g., ringworm), are *not* recommended for general use because the fumes are irritating to the respiratory tract of cats and human beings and may increase susceptibility to URTD rather than minimize it. Dilutions can be incorrect because of math errors. Veterinarians should doublecheck formulae used to calculate dilutions for all disinfectants, because concentrations too weak or too strong can increase URTD occurrence.

New products are becoming available. Recently, chlorine dioxide (e.g. Dentagen) was demonstrated to kill feline herpesvirus and calicivirus after a 10-minute contact time.[35] Chlorine dioxide (in stabilized form) is nontoxic, hypoallergenic, and less corrosive for surfaces than bleach according to the manufacturer. Other new products (e.g., Virkon S, Trifectant) containing potassium peroxymonosulfate kill herpesvirus and calicivirus.[35] They are less irritating to the respiratory tract, less corrosive to metal, less likely to be inactivated by organic matter, and work on carpet according to the manufacturer. Also, alcides are a new form of sodium hypochlorite purported to be less corrosive to metal, have a spectrum of activity similar to bleach, are more effective in the presence of organic material, and have low toxicity.[26]

Data regarding the efficacy of new products in shelters for disease prevention are predominantly anecdotal. Working under ideal circumstances (as those tested by manufacturers) may not translate into working or working well under less-than-ideal situations (as is true in many shelters). Adoption of new products into shelter CSD protocols should be accompanied with a plan to review their performance.

Once staff members understand why specific aspects of the CSD protocol are important, then they should be observed implementing the protocol regularly. Resourceful staff members sometimes devise short-cuts or forget the importance of certain procedures, and identifying these diversions from protocol can drop URTD rates. Similarly, identifying and correcting deviations from manufacturers' recommendations (e.g., errors in dilutions, disinfecting times) can reduce URTD.

The importance of cleaning and disinfecting to the prevention of disease in cats must be emphasized to staff members who may not understand disease etiology and transmission. Veterinarians usually are not involved in the development of cleaning and disinfection protocols because the protocols predate employment of the veterinarian, and these procedures are well described in publications from humane organizations. Veterinarians periodically should observe staff clean and disinfect, however, to familiarize themselves with the protocols, to identify departures from them, and to facilitate recommendations for changes, if necessary.

Ventilation: Evaluate the System

Despite the lack of evidence supporting aerosolization as a primary mode of transmission of herpesvirus or calicivirus infections,[36,37] upper respiratory infection rates frequently rise in shelters with inadequate ventilation. With poor ventilation, humidity levels can rise, which concentrates agents and ammonia from animal waste or fumes from disinfectants. Most small animal veterinarians are trained poorly to assess the functioning of ventilation systems and therefore ignore making recommendations for improvement. Therefore veterinarians working with shelters with high URTD rates are advised to consult with heating, ventilating, and air conditioning (HVAC) experts.[26] Ideal is someone with animal facility experience, who can evaluate the functioning of the ventilation system critically.[38]

To optimize the interaction with an HVAC specialist, veterinarians should understand what is ideal from a disease control viewpoint. Animal shelters require a minimum of 10 air changes per hour.[39] Air from areas housing sick cats should never be recycled through areas with healthy animals, and quarantine and isolation areas should be ventilated separately. Constant intake of fresh air and exhaust of circulated air is preferable to recirculating air within a facility (as the concentration of infectious agents is minimized). However, outside air often requires heating or cooling for animal and human comfort. Because heating and cooling are expensive, ventilation systems should control the recirculation ratio, which increases the proportion of outside air during URTD outbreaks and decreases it when disease rates are relatively low.[26] Temperatures optimally should be between 18.3° C (65° F) and 23.9° C (75° F), at the lower end for adults and the higher end for kittens.[8] Temperatures throughout a facility should be monitored periodically for micro-environments where extremes exist. For example, cats near windows may be subject to drafts in the winter and high temperatures in the summer if not shaded from the sun. Recommendations for relative humidity suggest levels between 30 and 70 per cent, but optimal humidity probably is closer to 35 per cent.[39] Wet surfaces dry more quickly, and the growth of molds and survival of pathogens are reduced.[26]

Veterinarians should recommend that fans run after cleaning until the environment is dry and that ventilation ducts and registers be cleaned regularly and dirty air filters be replaced. Despite poor training of small animal veterinarians with regard to ventilation systems, their knowledge of URTD agents and their epidemiology and their recognition of minimal ventilation requirements for animals can enable them to consult with HVAC experts to assess and improve the ventilation system of shelters.

Other Adjuncts to Reducing Agent Concentration: Consider the Use of HEPA Filters, Ultraviolet Light

Some shelters use adjuncts to ventilation to reduce the incidence of URTD such as ultraviolet lights or high-efficiency particulate accumulator (HEPA) filters. Both products are used widely in human medical and research facilities to reduce agent load. If used, both products must be installed properly and maintained by personnel experienced with the unique needs of facilities housing animals. Johnson maintains that stand-alone HEPA filters, although relatively inexpensive, are marginally effective and require frequent replacement of expensive filters, largely because of heavy hair contamination.[38] When installed as a component of some central systems, HEPA filters can remove all but micron-sized contaminates and require less frequent, expensive filter replacement.[38]

Ultraviolet radiation units require less maintenance, and when designed and located properly, can kill agents as small as viruses, making them a product worth considering in the control of respiratory agents. To what extent, if any, respiratory disease occurrence is reduced by the installation of either HEPA filters or UV units in shelters is not known. In existing shelters, it seems likely that first investing in improvements in other, less expensive components of CSD protocols may have larger payoffs in reductions of respiratory disease. The addition of HEPA filters or UV lights after these control measures have been optimized then may be considered.

ENHANCING HOST RESISTANCE

Reduce Stress: Minimize Stress in Animals and People

Stress in shelters results from many sources and can be physical, emotional, or environmental (see Chapter 76). Cats can enter shelters already stressed and shelters themselves are inherently stressful. Stress is important because it can lead to decreased immune function, increased susceptibility to disease, and reduced responsiveness to vaccination and treatment.[40,41] Many cases of URTD manifesting after about 7 days in the shelter probably are the result of herpesvirus recrudescence in cats stressed by entry into the shelter. Experimentally, herpesvirus-infected cats begin shedding virus about 7 days after a change in housing.[42] Effective stress management is essential to the success of any URTD control program.

Some stresses are unavoidable. For example, cats entering shelters injured, diseased, or malnourished already are stressed. Other stresses may be minimized or eliminated with careful attention to management and environmental factors contributing to stress. Many strategies can be adopted to reduce stress in sheltered cats. They include many of the factors discussed already (e.g, adequate temperature, humidity, avoidance of overcrowding) and many others (e.g., treatment of preexisting injuries or illnesses, humane handling, exercise, socialization, environmental enrichment).[43] Stress probably plays a far more important role in URTD frequency and severity than many shelter personnel appreciate.

Often not mentioned in conjunction with disease control in animals is the effect of stress on animal caretakers. Anecdotal stories suggest that when handlers are stressed, stress can be transmitted to the animals. Rough handling or poor attention to detail (such as cleaning), for example, probably contributes to poor overall animal care. Humane care and attention to staff and volunteers should be a part of the feline URTD control program.

Nutrition

Some shelters acquire food through donations from the public and feed whatever is readily available. Poor nutrition itself is a form of stress and can lead to reduced immune function, increased susceptibility to URTD, and increased time for recovery. It is beyond the scope of this chapter to provide a detailed discussion of feeding shelter animals, but resources exist to establish a good nutritional program.[44]

Vaccination: Recognize That Vaccination Alone Will Not Reduce URTD

Although vaccination probably is foremost in the minds of most veterinarians in their attempts to enhance host resistance, it may be of minor importance in feline URTD management in shelters. Despite the perception, based on experience in private practice, that upper respiratory vaccines (addressing herpesvirus, calicivirus, and *Bordetella bronchiseptica*) are efficacious in minimizing feline URTD, this impression probably is more a function of lack of (or low dose) exposure in client-owned cats, than a testimony to the efficacy of vaccination for URTD.[45] Respiratory vaccines do not protect against infection but are designed to reduce the severity of clinical disease.[11] The

effectiveness of calicivirus vaccination is compromised further by the recognition that the antigenicity of FCV field strains has changed since the introduction of the FCV-F9 vaccine strain more than 2 decades ago.[46] FCV isolates antigenically different from that used in the vaccine were recovered from most cats experiencing vaccine breakdowns.[47] The appearance of new, sometimes highly virulent strains of calicivirus should be of concern to shelters[48,49] (see Chapter 1). Vaccinations for URTD probably have limited usefulness in the shelter environment where cats are stressed, may be unvaccinated or previously unexposed, are housed in close proximity to other cats, and are exposed to contaminated fomites. Shelters frequently report dramatically different disease rates, despite the use of similar vaccination protocols. Unfortunately, although much research is available regarding the efficacy of upper respiratory tract vaccines under controlled conditions, little is known about the performance of these same vaccines in animal shelters.[45]

Lacking extensive data regarding the efficacy of vaccination in shelters, current guidelines are based largely on preventive medicine principles, anecdotal reports from shelters, and vaccine research outside of shelters. Under controlled conditions, topically administered modified live virus (MLV) vaccines (intranasal [IN] or intranasal/intraocular) for herpesvirus and calicivirus induce a rapid, local immunity within 1 to 4 days in immunologically naïve cats and kittens (without interference from maternal antibodies).[5,41,45] Additionally, topical vaccines can be used safely in kittens as young as 3 weeks of age, and doses can be split for young kittens without an apparent loss of efficacy. In theory, topical respiratory vaccines would appear to be the products of choice in shelters. Unfortunately, this is not necessarily the case. Topical respiratory vaccines can elicit mild clinical signs; therefore some shelters avoid them be-cause distinguishing vaccine-associated signs from those resulting from natural infection is difficult. Also, some shelters, especially those without resident veterinarians or veterinary technicians, find topical administration more difficult than injections. Among shelters having used topical products, some report reductions and others report increases in URTD occurrence. The IN vaccination for *B. bronchiseptica* induces a nonspecific immunity that protects temporarily against other respiratory pathogens.[50] Anecdotally, some shelters experiencing *B. bronchiseptica* outbreaks in their cats report significant declines in signs and in kitten mortality after the introduction of *B. bronchiseptica* vaccine. On the other hand, Schultz and Ford report that in their experience this has not been true.[45,50]

In open admission shelters, parenteral vaccines (killed or MLV) probably have limited value. Parenteral vaccines are available for FHV-1, FCV, *B. bronchiseptica,* and *C. felis*. Among immunologically naïve cats, the time from parenteral vaccination to effective immunity is 1 to 2 weeks in adults and longer in young kittens and for killed products.[41,51,52] In open admission facilities, most of these cats have either been adopted or become sick before vaccine-induced immunity can occur. Among previously exposed cats (by vaccination or natural infection), vaccinating with a parenteral product boosts immunity within 24 to 72 hours, and if vaccination precedes exposure, should reduce the frequency and severity of disease.

Results from shelters (although sparse) are becoming available. Based on work conducted by his laboratory, Schultz recommended an IN calicivirus and herpesvirus vaccine in relatively low-stress, low-density shelters.[50] In high-density, high-stress shelters, however, he suggested that a killed, parenteral vaccine may be preferred. He speculated that in high-density, high-stress shelters, the combination of stress and use of a MLV product may lead to sufficient immunosuppression to cause vaccine-induced disease.

Results from a vaccine trial conducted in one shelter involving 57 cats indicated that the combination of an IN and MLV parenteral vaccination protocol reduced respiratory signs approximately 66 per cent compared with parenteral vaccine alone, which suggests the concurrent use of both types of vaccines.[53] In an observational study of 701 litters of kittens, 531 kittens and 2203 adult cats, conducted in one shelter for 50 weeks, IN vaccination reduced signs twofold in litters of kittens and individual kittens compared with unvaccinated kittens during the first 5 days of shelter residence. Interestingly, IN vaccination did not reduce signs in cats more than 7 months of age during the first 5 days, but parenteral vaccination with a MLV vaccine reduced the frequency of URTD approximately 60 per cent in cats with more than 5 days residence in the shelter compared with cats receiving IN vaccine during the same period.[54]

Strong recommendations based on studies are premature. Much research remains to be done regarding vaccination protocols for URTD in cats in shelters. Until more research is available, veterinarians must make choices based on available knowledge about performance of vaccines in other situations, principles of immunology and, perhaps most importantly, experience in their own shelters.

Drug Prophylaxis: Drugs Are No Substitute for Hygiene, Stress Reduction

Some shelters administer L-lysine or interferon routinely to resident cats in an attempt to reduce the frequency or severity of URTD. In vitro, L-arginine, an amino acid, is essential for the successful replication of the human herpes simplex virus (HSV-1) and FHV-1.[55,56] L-lysine antagonizes L-arginine and reduces HSV-1 and FHV-1 replication in vitro when the ratio of lysine to arginine is high.[56] Oral treatment with L-lysine of human beings with recurrent HSV-1 lesions reduced lesion recurrence rates and severity and enhanced recovery times.[57,58] A few trials in cats are emerging,[59,60] but the usefulness of administering L-lysine to shelter cats is, as yet, unclear. If it is effective, its use is specific to herpesvirus infections and the drug would need to be administered before signs developed. Current data suggest that the incidence of herpesvirus infections would not be reduced, but the severity and period of shedding may be decreased.[59,60]

Interferons are cell-derived proteins that inhibit the synthesis, assembly, and release of a wide range of DNA and RNA viruses. Early studies demonstrated antiviral activity of human and feline interferon against FHV-1 and FCV-F9[61] in vitro but failed to demonstrate its effectiveness in cats to reduce severity of disease, except at high doses.[62] In a recent report, FHV-1–infected cats treated once daily with 25 U of natural human interferon alpha (IFN-α) early in the course of disease experienced less severe disease than control cats, but had no effect on shedding.[63] The effectiveness of interferon in shelter cats to lessen disease severity has not been evaluated. Until efficacy has been established, use of L-lysine or interferon in shelter cats seems unjustified scientifically.

MINIMIZING EXPOSURE

Isolation: Separate Sick and Healthy Cats

Because cats with clinical signs are most efficient at transmitting disease, they must be isolated from healthy animals. Ideally, sick cats should be housed in a separate facility. Because this is not feasible for most shelters, an isolation room or infirmary (ventilated separately) is the goal.[8] A separate bank of cages for sick cats in the same room as healthy animals or a hallway is *not* an acceptable approach to isolation. This approach does not prevent accumulation of agent in the environment and does not remind people of special procedures (e.g., hand-washing, changing of smocks) associated with leaving an isolation room. Similarly, it does not limit access to designated people, and it does not encourage separate cleaning supplies, dishes, and litter pans. Treatments should be performed in the isolation room or infirmary because transporting sick cats to other areas of the shelter facilitates spread of disease.

Quarantine: Separate Potentially Infected Cats and Healthy Cats

Because cats can be incubating respiratory disease when they enter the shelter, they should be quarantined 10 to 14 days before being introduced into the adoption areas[5] in limited admission facilities. Calicivirus can be shed for long periods of time, but it is impractical for shelters to quarantine cats at least 4 weeks postinfection to minimize adding shedding cats to adoptable animals (as has been recommended for catteries). Because length of time in an open admission shelter is correlated so strongly with risk of URTD,[53,54] however, cats should *not* be quarantined in these facilities. Rather, they should be examined, and if healthy, vaccinated and put up for adoption as quickly as possible. In my opinion, fewer cats will become ill than if a quarantine protocol exists.

Foster Care: Remove Susceptible Cats from Exposure

Investment in an extensive, well-managed foster care program is an important tool for reduction of URTD and potentially for hastening recovery of some cats with URTD. Many shelters routinely put kittens and nursing queens and kittens without queens into foster care as soon after arrival in the shelter as possible (after worming and vaccination). The less time in the shelter (where URTD agents are concentrated), the smaller the risk of exposure will be. If fostered kittens can be taken directly to off-site adoption areas, that is ideal. If not, once returned to the shelter, healthy kittens should be placed for adoption (as quickly as possible) in housing separated from sick and adult cats (which may be carriers). Kittens returned to the shelter from foster care at 7 to 9 weeks of age are losing (or have lost) their maternal immunity and are highly susceptible to URTD. Foster care also can be used for other cats at high risk of URTD or for cats with URTD that are slow to respond to treatment in the shelter. Foster care can be an important component of a good URTD-control program, but foster care providers *must* be well trained and the program well managed, or disastrous situations can arise.[64]

MINIMIZING TRANSMISSION

Housing and Traffic Patterns

Cats should be housed as far away from barking dogs as possible. Two-tiered caging probably is best when cats are housed in individual cages. Additional tiers make effective cleaning and disinfection difficult and reduce viewing of cats housed in the top tier in the adoption room. Wood (or other porous materials) for caging or shelves should be avoided unless they have been sealed appropriately to prevent the persistence of pathogens in these materials. Keeping facing cages at least 4 feet apart prevents droplets propelled by sneezing from crossing from one bank of cages to another. Also, cages should not be placed in drafty areas or in other areas with temperatures outside the desirable range.

Many shelters are moving away from individual cat-housing to group-housing (whether that be in small groups [two to eight cats] or larger colonies). How this change will affect the incidence of URTD in these shelters is unknown. Some have speculated that group-housing will reduce URTD because the cats will be less stressed, once the group adjusts. The opposite also is possible; that is, as more cats are housed together, stress will increase, and the likelihood of transmission also will increase. Veterinarians in shelters making this transition are encouraged to keep records regarding the incidence before and after the change, which allows them to evaluate data that are directly pertinent to their circumstances.

Because fomites (e.g., people and objects carried from room-to-room and cage-to-cage) are important modes of transmission, the flow of traffic should be from healthy to sick and most susceptible to most resistant. For example, kittens should be the first animals encountered in adoption rooms. This minimizes the probability that the public will handle adult cats shedding URTD agents and then carry those agents to the kittens. Many shelters have potential adopters encounter adults first, however, as they seek to market adult animals preferentially that have a lower probability of being adopted. In reality, if and by how much URTD is reduced by placing kittens before adults is unknown.

As with most decisions in shelters, competing interests of the shelter must be considered when designing housing protocols. Balancing limited resources, stress reduction, preventive medicine, adoption, and other concerns is the constant challenge of the shelter veterinarian.

SYSTEMATIC DEVELOPMENT OF A URTD CONTROL PROGRAM

When performing a physical examination, designing a treatment protocol, or investigating a disease outbreak, veterinarians should use a systematic method. This ensures that important observations or components are not overlooked and a logical plan underpins decisions. A systematic approach to evaluating (or developing) a URTD-control program similarly must be adopted. The previous discussion provides the keys to this process.

The systematic approach is multifaceted.

(1) It includes establishment of the current status of the URTD burden in the shelter and various subgroups. A good surveillance program is essential.

(2) Goals and a timeframe to achieve them should be explicit and realistic. For example, upgrading of the ventilation system

in the next 3 years may be a goal. Similarly, having determined that the current incidence of URTD in the shelter is 30 per cent annually, a goal could be to reduce the incidence by 3 per cent over the coming year.

(3) The facilities (including ventilation and temperature regulation throughout the shelter) and current management practices affecting URTD should be understood *thoroughly*. Taking the time to develop this understanding can suggest relatively easy changes to current protocols, or even relatively inexpensive changes to the facilities that could reduce disease immediately. For example, staff members of one shelter, after taking inventory of their physical facilities, realized that their garage had become a disorganized, catch-all area. Animal control vehicles had not been housed in the garage for years. For a small investment, this area was converted into cat holding areas to reduce crowding and provide better isolation for kittens before going to foster care.

(4) Explicit identification of those factors, policies, and concerns that are impediments to achieving the goals facilitates development of pre-emptive strategies to minimize or eliminate their impact. For example, if the shelter decides to introduce IN vaccination as a component of their URTD-control program, then staff must have *quality* training and supervision to administer the vaccine and be provided with guidelines to distinguish vaccine-induced signs (using time of vaccine and severity of signs) from signs resulting from natural infections.

(5) Plans to achieve the goals can be developed and implemented explicitly. In some shelters the plans may not look different from what is already being done. What may look different, for example, is the addition of a discussion in every staff meeting of how the URTD program is going and difficulties that staff may be experiencing. This discussion would be an opportunity to continue to team-build and provide feedback of the data collected so far.

(6) Data should be analyzed and reviewed. Initially, accurate progress assessment may be difficult because of seasonal differences in URTD occurrence and population dynamics (e.g., proportion of kittens). Monthly trends can be identified, however, and potential reasons for their fluctuation discussed. Over time, comparisons would be made between URTD rates this year and those the previous year, between different areas of the shelter (e.g., group-housing versus individual cage housing), and other comparisons. Feedback provided to staff, volunteers, and board members is further incentive to continue. Meeting goals is cause to celebrate and reconfirm efforts to meet new goals. If goals are not met, then reasons for not reaching them can be addressed. The data document to the executive director and board members why URTD control should be a high priority, and furthermore suggest where resources can be directed most effectively.

SUMMARY

Shelters have an ethical obligation to provide the best care for those animals entrusted to their care. Establishing control programs to minimize the incidence of URTD in shelter cats is an important component to providing quality care. Too many otherwise adoptable cats are euthanized for URTD, too many suffer, and too many resources are devoted to treating affected cats that could be used to reduce the numbers of cats entering shelters.

URTD cannot be eliminated because of the highly contagious nature of the agents, their carrier states, and the lack of vaccines that prevent infection and shedding. The incidence, however, can be reduced. Anecdotally, shelters exist with high and low rates of URTD. The factors that explain these differences are not fully understood. Unfortunately, no studies exist currently that indicate where the emphasis with regards to control should be put. Probably, the prioritization depends on the type and layout of facilities, number of animals handled, circulating agents, season, and other factors. Shelters must be willing to invest time and effort evaluating what works best in their situation. A URTD surveillance system is essential, enabling shelters to understand the magnitude of URTD in their facilities and making it possible to monitor the effectiveness of changes in control measures on disease rates.

Shelter staff and veterinarians must reserve time in their hectic schedules to *plan*. They should develop a protocol that deals specifically with feline URTD in their facility and then evaluate the effectiveness of that protocol. URTD control requires vigilance and persistence. Goals should be realistic and small steps toward achieving them are allowed. Borrowing from a statement made by Dr. Kate Hurley, Director of the Shelter Medicine Program at the School of Veterinary Medicine, University of California, Davis: Development of an effective URTD control program *is an evolving process, a dialogue between where a shelter is and where the shelter would like to be.* Attaining an effective program requires a partnership between veterinarians, staff, volunteers, administration, and board members to be successful.

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Chapter 78

OSTEOARTHRITIS

Vicki J. Adams

Osteoarthritis (OA) is a well-recognized problem in human beings and dogs. OA is considered to be the most common non-inflammatory arthropathy of human beings; it affects approximately 10 per cent of men and 18 per cent of women over the age of 60.[1] Variable figures have been reported on the frequency of occurrence of this disorder in dogs, but OA is estimated to affect up to 20 per cent of the canine population.[2] OA in cats is not as well recognized. As early as 1997, Hardie stated, "Osteoarthritis in cats is not a well-documented disease."[3] She then continued, "Although cats are usually included in reviews of joint disease in small animal patients, dogs are the primary focus of the discussion." This is still true today and similar statements have been repeated in textbooks of internal medicine, surgery, and small animal practice. A typical textbook entry is as follows: "Osteoarthritis is diagnosed in dogs far more frequently than cats."[4] Treatment sections in such texts are concerned mainly with dogs, and cats are mentioned rarely. More recent publications have included more information on treatment of OA in cats. For example, McLaughlin reported a dosage for the use of one drug in cats, and two of the 87 references at the end of the chapter were on cats.[5]

The lack of awareness of feline OA in the past most likely has been due to a combination of factors that include the small size of cats relative to other species, the ability of cats to compensate for orthopedic conditions by redistributing weight-bearing to unaffected limbs, and normal feline behavior that hides signs of lameness and often precludes gait analysis.[6] The increasing recognition of OA in cats likely is due to an increasing awareness and understanding of the importance of pain recognition and treatment in cats and the role that OA plays in the experience of chronic pain.

A few definitions are helpful to understand the terms used in this chapter. OA or degenerative joint disease (DJD) is a disorder of moveable joints characterized by degeneration of articular cartilage and the production of new bone at articular margins. The emphasis is on the degenerative and progressive nature of the condition associated with loss of cartilage. DJD is a term used to encompass all changes seen in OA. The terms OA and DJD have been used and, for practical purposes, can be used interchangeably. DJD can be defined clinically, radiographically, and pathologically, and probably represents the end-stage of a variety of joint problems rather than a distinct clinical entity. The term osteoarthritis is used by some clinicians who wish to place emphasis on the inflammatory nature of the condition. However, as synovitis frequently is minimal, others prefer the term osteoarthrosis to indicate a pathological condition that is not an acute inflammatory process. Secondary joint disease also may be used to describe the situation in which prior initiating factors have been identified, including such conditions as fractures and ligament ruptures. Infectious and inflammatory arthritides are syndromes associated with more acute inflammation in the affected joints.

Although OA may not be as well documented in cats as it has been in other species, it is becoming essential for practitioners to recognize the clinical signs associated with DJD, particularly as cats now are enjoying longer lifespans. The purpose of this chapter is to present what is known about the epidemiology, pathogenesis, etiology, diagnosis, and treatment of OA in cats.

EPIDEMIOLOGY

The prevalence of OA in cats has not been well documented, with estimates from published retrospective studies ranging from 4 to 90 per cent. Prevalence estimates are higher in those studies that looked at older cats. One of the first reports on the frequency of occurrence of OA in cats was made when radiographs of 68 cats over 12 years of age were reviewed for a variety of diseases. In this study at North Carolina State University, 14 cats had radiographic evidence of OA to give a prevalence of 21 per cent, with an additional 39 cats identified with spondylosis to give a combined prevalence of 78 per cent.[3] In a later study with additional cases, Hardie found radiographic signs of DJD in 90 of 100 cats greater than 12 years of age to give 90 per cent prevalence.[7] A survey of veterinary practices in the United Kingdom revealed that 10 cases out of 271 (3.7 per cent) presented to first opinion practices for evaluation of orthopedic disease were diagnosed with arthritis. However, this study does not specify the age of the cats nor does it distinguish acute arthritis from DJD.[8] A more recent practice survey in the United Kingdom identified 63 of 292 cats greater than 1 year of age that had a diagnostic radiograph of at least one limb synovial joint that showed evidence consistent with OA to give a prevalence of 22 per cent.[9] Finally, a

study by Clarke and others found that 74 of 218 cats showed radiographic evidence of DJD to give a prevalence of 34 per cent, although only 36 of the 74 cats had appendicular OA.[10] The most commonly reported affected joints were the elbows and shoulders.[7]

PATHOGENESIS

Diarthrodial, or moveable, joints are made up of articular cartilage that is lubricated and nourished by synovial fluid. A synovial membrane lines joints, contains pain receptors, and secretes synovial fluid. Approximately 80 per cent of articular cartilage is water; type II collagen and proteoglycan matrix make up the remaining 20 per cent.[4] Chondrocytes synthesize and degrade proteoglycan continuously in normal cartilage. Disturbances in both cartilage and synovial membrane structure and function can occur with OA. Cartilage disruptions observed in OA include increased synthesis and degradation of proteoglycan, increased cartilage hydration, loss of collagen integrity, loss of tensile strength, fibrillation, and eburnation. Synovial membrane abnormalities observed in OA include synovitis with mainly mononuclear cell infiltration and inflammatory mediator release into synovial fluid.[4] The release of degradative cartilage enzymes is pivotal in the pathology of OA and results in irreversible cartilage damage. Cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF-α) cause catabolic cartilage changes by promoting the production of degradative cartilage enzymes. Other mediators such as insulin-like growth factor (IGF), transforming growth factor β (TGF-β), and interleukin-6 (IL-6) are associated with increased proteoglycan synthesis. Sources of inflammatory mediators include chondrocytes, synovium, and mononuclear inflammatory cells.[11]

The pathogenesis of OA involves cartilage erosion and new bone production. The main biochemical change in cartilage that leads to erosion is a loss of proteoglycans combined with normal collagen content. Although proteoglycan synthesis is increased in OA, destruction and net loss of proteoglycan from matrix also are increased, which leads to loss of structure and function.[11] Proteoglycans have a vital function in the preservation of cartilage integrity. A proteoglycan molecule consists of many repeating chains of glycosaminoglycans. The glycosaminoglycans are mainly chondroitin sulfate and keratin sulfate. Hyaluronate binds to the proteoglycan to form an aggregate. Articular cartilage is composed of a loose collagen network that contains chondrocytes and high molecular weight proteoglycan-hyaluronate aggregates to form a stiff, gel-like substance. The high molecular weight aggregates have an osmotic attraction for water molecules. Water molecules held in the cartilage exert outward pressure to maintain the stiffness of the collagen network, and this stiffness results in lubrication of the cartilage at high loads. As compressive loads move the glycosaminoglycan chains together, water is displaced and the negatively charged glycosaminoglycans resist further compression. In this way, cartilage is viscoelastic and is able to deform and re-form with normal repetitive loading.[5]

The proteoglycan loss of OA occurs in spite of increased proteoglycan synthesis and is due to a change in the nature of the proteoglycan that is synthesized. Chondroitin sulfate chain length decreases and also glycosaminoglycan content changes. The proteoglycans contain relatively less keratin sulfate in relation to chondroitin sulfate, and more of the chondroitin sulfate is present as chondroitin-4-sulfate rather than chondroitin-6-sulfate.[11] The decrease in proteoglycan content of osteoarthritic cartilage also is thought to result from enzymatic proteoglycan breakdown. Controversy exists regarding whether the degenerative enzymes are extrinsic (i.e., arising from synovial tissue) or intrinsic (i.e., arising from the cartilage itself). Proteases, particularly the neutral serine proteases and metalloproteases, are thought to be mediators of articular cartilage destruction. Degradation of the proteoglycans leads to dramatic decreases in the molecular weight of the proteoglycan-hyaluronate aggregates, and this leads to loss of water from the articular cartilage. The loss of water combined with the loss of stiffness of the collagen network increases the probability of mechanical disruption of cartilage.[5] In contrast to what is known about the mechanisms of cartilage degeneration, much less is understood about the mechanisms of new bone production in DJD. Osteophytes have been recognized as early as 3 days after experimental induction of cranial cruciate ligament rupture in experimental models.[11] The relationship between cartilage degeneration and osteophyte formation is not clear.

ETIOLOGY

OA can be a result of primary or secondary disorders. Primary causes rarely are identified, and secondary OA resulting from altered joint biomechanics accounts for most cases in veterinary patients.[12] Secondary causes include congenital and developmental disorders such as osteochondrosis dissecans (OCD) and hip dysplasia, and acquired causes such as cranial cruciate ligament injury, patellar luxation, joint instability resulting from ligament injury, and malunion of intraarticular fractures.[11] As indicated throughout this chapter, DJD likely represents the end-stage of a variety of pathological processes and etiology may be multifactorial in many cases. The most important factor generally is thought to be trauma either in the form of a single serious injury or as low-grade "wear and tear" that occurs normally over time.[4] Abnormal joint anatomy that results in instability may accelerate the damaging effect of normal use and wear. Because OA is associated with symptoms of chronic pain in human beings, pain behavior in cats must be characterized to facilitate pain assessment.

ASSESSMENT OF PAIN IN CATS

The assessment of pain in pets relies on observation and the interpretation of behavior. Pain assessment by pet owners familiar with the personality and normal behavior of their pet is an important part of the process. A complete history, physical examination, and appropriate laboratory tests also are required to reveal any underlying illness that may explain the signs of pain. Physiological parameters such as heart rate, respiratory rate, blood pressure, and body temperature are unreliable indicators of pain.[13] The insidious onset of signs of chronic pain in cats, and the similarity of these signs to those of other chronic or age-related conditions, make the recognition of pain in cats difficult for both owners and veterinarians. Common behavioral patterns that indicate pain in cats are shown in Table 78-1. A cat in pain may vocalize less than normal or may growl or hiss when approached or touched. Vocalization associated with pain may be continuous or intermittent, or it may occur only when the cat is touched. Cats in pain may have a tendency to become reclusive. They may have a stiff posture or they may

Table 78-1 | **Behavioral Signs of Pain in Cats**

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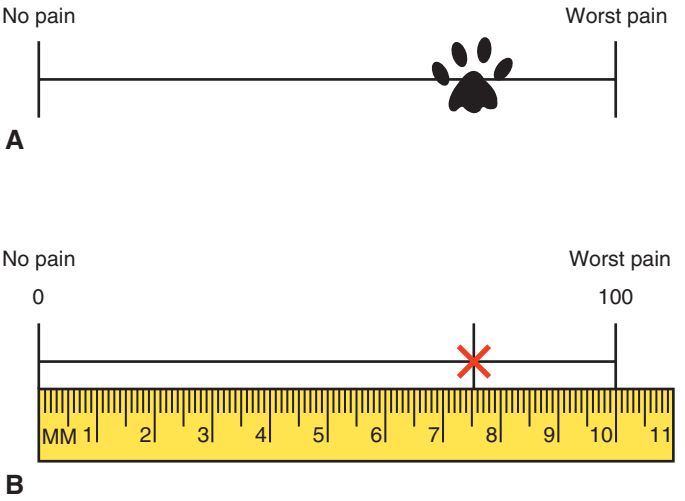


Figure 78-1. Visual analogue scale (VAS). **A,** The ruler as presented to a patient or pain assessor. **B,** Using a metric ruler to measure the amount of pain experienced or perceived as distance in millimeters from the 0 end of the scale; in this example, the pain level is 75.

sit in a hunched position, not stretching as they normally would. A cat in pain is likely to be less active, and it may be reluctant to move, particularly to run or jump.[13]

Many pain-scoring systems in human medicine have been used to assess pain in human patients and also to assess efficacy of analgesics in clinical trials. Historical and current pain classification systems based on anatomy, body system, underlying cause, severity, duration, behavior, and expert opinion have been inadequate to provide the type of information required to prescribe targeted and effective treatment in human beings. These systems commonly have used verbal rating scales, simple descriptive scales, and numerical rating scales that tend to rate pain on a four-point scale as none, mild, moderate, or severe. These scales are subjective and lack sensitivity. One report states that a 10- to 20-point scale is required to assess chronic pain intensity in human beings.[13] In animals, the concern primarily has been the diagnosis of the primary disease causing pain. The Ontario Veterinary College in Canada uses a 0- to 10-point scale with descriptors as a teaching tool to help students recognize, evaluate, and treat pain in dogs and cats.[13] A scale for the assessment of pain in dogs undergoing ovariohysterectomy[14] was adapted from human pediatrics.[15]

Visual analogue scales (VAS) have been used in human medicine as a method for patients or observers to report how much pain they are experiencing or perceiving across a continuum. From the perspective of the patient, the spectrum of possible pain experienced appears continuous. Pain occurs across a spectrum, and it does not occur in discrete values as the use of categories may suggest. The VAS uses a ruler that is usually 100 mm in length with only a description of the limits of pain (no pain, the worst pain possible) at each end of the scale (Figure 78-1). The patient or pain assessor places a mark on the line where the experienced or perceived pain falls. Then a measurement is made in millimeters from the 0 end (no pain) of the scale to the point marked on the line. This method has been shown to be reliable and sensitive in studies that assess pain and efficacy of analgesia in studies of human beings, dogs, and cats.[13,16,17] A refinement of this approach is the dynamic and interactive VAS (DIVAS), which offers an alternative to the simple VAS. The DIVAS approach combines a visual appraisal of spontaneous behavioral signs indicative of pain with a qualitative assessment of response to an acute stimulus. The acute stimulus could be palpation of a suspected affected area: if the affected area is sensitive, palpation of the area will elicit pain and behavioral signs indicative of pain.

Interaction between the observer and patient may be used to assess the overall state of a patient more fully. DIVAS has been used to assess and compare the efficacy of analgesics for control of postoperative pain in cats. In a study comparing two analgesics for postoperative pain control after routine ovariohysterectomy, the DIVAS method was used to assess pain and sedation. Cats were first assessed visually while undisturbed. Then they were approached and the assessor talked to the cat, opened the cage door, gently handled and encouraged the cat to move about, and then palpated the area of the incision while the cat's reaction and behavior were observed.[18] The DIVAS method also has been used with a mechanical algometer to obtain nociceptive threshold values to assist in assessment of pain in dogs undergoing ovariohysterectomy.[19] Although the use of a VAS or DIVAS as part of a routine clinical examination to assess pain in cats or dogs has not been reported, these scales offer a more objective method for pain assessment, particularly to monitor changes in pain levels associated with OA.

DIAGNOSIS

The diagnosis of OA is based on a combination of history, physical examination, and radiographic findings. Cats with OA may present to the veterinarian for a variety of owner complaints, and with a range of historical or clinical signs that may or may not include lameness. A change in temperament that leads to depression, anorexia, or aggression is common. A suspicion of OA may be present after history and physical examination. Radiographs and joint fluid analysis confirm the diagnosis although the latter is rarely necessary. Confusing OA with polyarthropathy resulting from infectious or noninfectious inflammatory causes is rare.[11]

History

The history may reveal a loss of appetite, weight loss, failure to groom, reluctance to jump or move about, or even overt

Table 78-2 | **Clinical Signs of OA That May Be Apparent from the History and Physical Examination**

Decreased appetite
Weight loss
Failure to groom
Reluctance to move
Refusal to jump
Lameness
Pain on joint palpation/manipulation
Joint crepitus, swelling, effusion
Decreased range of motion
Muscle atrophy

lameness (Table 78-2). Weight loss and house soiling accidents may have occurred as a result of diminished ability to reach the food dish or litterbox. The hair coat may be dull or matted because of lack of grooming. Apart from a noticeable gait abnormality, these signs are vague and could be indicative of a number of health problems. A history of previous trauma that may lead to joint instability or disturbance of the articular cartilage is important. Lameness may be present in one or more legs, with occasional or persistent, and usually partial, non–weight-bearing lameness is noticed. Careful questioning of an owner elicits information about what the types or extent of activities the cat has or has not been doing. Questions should be worded carefully, using "does do" or "performance" wording rather than "can do" or "capacity" wording. For example, "Does your cat jump up on windowsills?" should result in a more useful response compared with, "Can your cat jump up on windowsills?," using a four-point scale of ability to record the owner's response:

without any difficulty – with some difficulty – with much difficulty – unable to do

A questionnaire with a rating scale and pain descriptors, given to an owner or used as part of a clinical examination, is one tool that can help identify and localize pain in their cat.

Clinical Signs

Evaluation of the cat should include a general physical examination and a specific orthopedic examination. Gait observation should take place before the cat is handled and may require covert observation of the cat through a window or from behind a partially closed door while allowing the cat to move about in an examination room.[6] Gait abnormality may be obvious or not so obvious. Lameness may have been observed by the owner or may be apparent when the cat is watched moving around the examination room. Lameness may be reported to be a morning stiffness that improves with activity as the cat appears to warm out of it, or it may worsen after vigorous activity. Examination of the joints with the cat standing allows palpation of joints and muscles. Joint effusion may be present and decreased range of motion also may occur. Muscle atrophy may be present, and this can be marked. Muscle atrophy around the thighs and over the spine of the scapula may be better appreciated in the standing cat.[6] Gentle restraint in lateral recumbency facilitates the remainder of the orthopedic examination and may require light sedation in some cats, depending on the individual's temperament. Reduced range of motion and joint effusion are good indicators of a joint problem. Manipulation may reveal pain and/or crepitus. Joint laxity may be especially apparent in the hip and knee. Clinical examination may reveal one or more of the following signs suggestive of a joint problem such as OA: pain on palpation or manipulation of one or more joints, and joint crepitus or laxity, with or without swelling or effusion (see Table 78-2).[3,4,6,7]

Arthrocentesis and Synovial Fluid Analysis

Joint taps may be used to help rule out other causes of joint disease. Although joint fluid analysis rarely is needed to diagnose OA, it is a rapid method of ruling out infectious and inflammatory causes. Most cats with OA have normal noninflammatory joint fluid or only a minimal increase in the number of mononuclear cells. Cats with progressive polyarthropathy have inflammatory, nonseptic joint fluid that is discolored, cloudy, or flocculent, and contains more than 5000 cells/μL with a large proportion of neutrophils and protein level greater than 5 g/dL.[20,21]

Radiographs

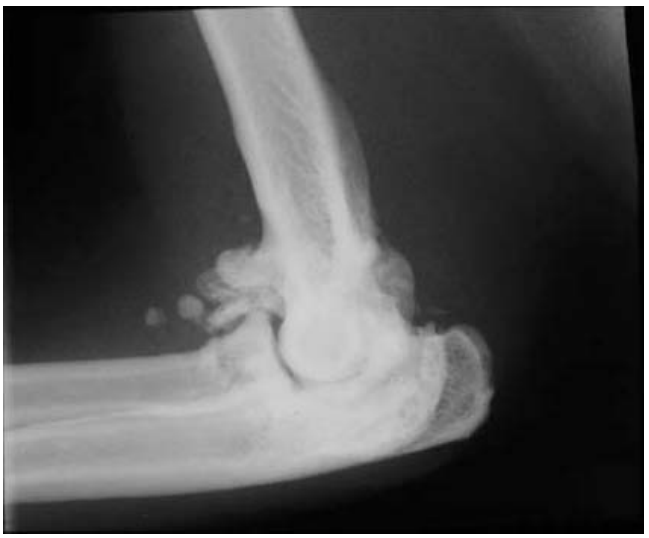
Good quality radiographs with the correct exposure for bone and joint evaluation are essential to allow detection of subtle evidence of OA. Radiographs should show signs of DJD, which may include joint effusion, soft tissue swelling, thickened joint capsule, narrowing of joint spaces, subchondral bone sclerosis, osteophytes/enthesophytes, new bone formation, and bone remodelling (Figure 78-2).[11,22] New bone formation is a response to joint instability, and in soft tissues it manifests as periarticular lipping. Subchondral bone sclerosis is indicative of thinning of the articular cartilage. Periarticular fibrosis and changes in bone shape also may occur. If radiographic changes are minimal, then a systemic disease, infectious arthritis, or nonerosive immune-mediated arthritis may be causing the clinical signs.

DIFFERENTIAL DIAGNOSIS

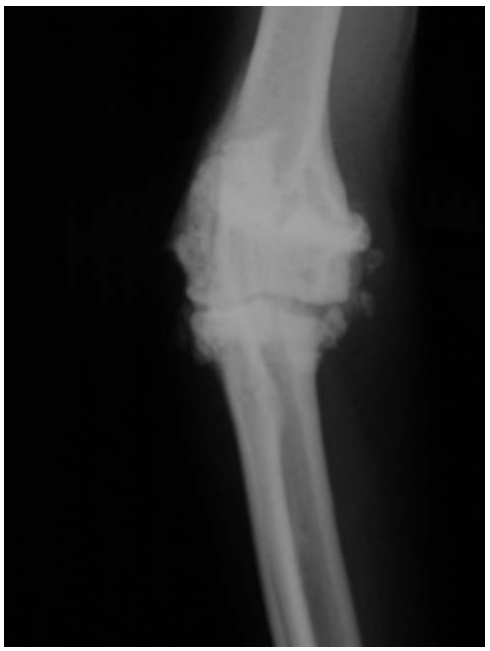
Differential diagnoses for OA include inflammatory causes of arthritis (infectious and immune-mediated), neoplasia, and, depending on one's definition, DJD secondary to known prior trauma, congenital malformations, or acquired joint instability. A published symposium provides an overview of the diagnosis and treatment of inflammatory joint disease.[23] Feline progressive polyarthritis is the most common inflammatory joint condition seen in cats. The disease is thought to be immune-mediated with two well-described forms, erosive and proliferative, although many cases may not have radiographic evidence of either proliferative or erosive changes.[20,21] Old cats with multiple diseases and concomitant OA may cause confusion, but if the other diseases are well managed and the cat continues to show signs consistent with pain resulting from OA, a therapeutic trial to treat the OA may be considered.

TREATMENT

OA is an irreversible progressive disease that cannot be cured by medical treatment. Having said this, the goals of treatment are to reduce joint pain, increase joint mobility, and reduce cartilage destruction to improve quality of life.[3,5,24] Treatment aimed at relieving pain may include surgical and/or medical



A



B

Figure 78-2. A and **B,** Radiographs showing characteristic changes of osteoarthritis in cats.

management in addition to changes to the environment. Surgical management of certain cases of secondary OA should be considered; for example, OA secondary to osteochondrosis dissecans, cranial cruciate ligament injury, and coxofemoral joint arthritis as a result of femoral neck fracture or hip dysplasia. Surgery in these types of cases can be expected to slow down the progression of OA and provide pain relief. Although they often are considered to be salvage procedures, femoral head and neck excision and distal joint arthrodesis can provide good results with respect to pain management.[24]

Medical treatment for the management of OA in cats follows that used in other species and may include weight loss for obesity, controlled moderate exercise, modification of the environment, and pain control. Although the conceivable importance of weight control in the treatment of OA and obesity cannot be overemphasized, weight loss can be difficult to achieve and it requires good owner education and cooperation (see Chapter 19). On the other hand, some older cats may have a problem maintaining weight. This worsens if they stop moving and energy levels decrease.[3] Gentle exercise such as controlled leash walks and swimming while avoiding strenuous activities is reported to be beneficial in dogs. However, controlled exercise of cats is difficult to encourage, although some cats may allow owners to perform physical therapy such as passive range-of-motion exercises.[24]

Pain control via environmental changes requires recognition of situations that cause the cat to experience pain. Assisting owners to identify activities that exacerbate their cat's problem may help to minimize episodes of pain and/or lameness. For example, realizing the cat has difficulty jumping up on a counter to eat would result in moving the food dish to a location more accessible to the cat. Other forms of environmental modification may include the use of ramps or graduated steps to discourage the cat from making large leaps up or down and to encourage the cat to move about easily without making the daily routine an obstacle course.[3] Limiting the need for the cat to jump, for example, onto a windowsill to go outdoors may help the cat be more comfortable.

Pain control also involves the administration of medications with antiinflammatory and/or analgesic effects, including the nonsteroidal antiinflammatory drugs (NSAIDs), other analgesics, and nutritional supplements.[5] Once treated, post-treatment assessment of the cat's perceived pain and activity levels can help to determine efficacy of therapy. The cornerstone of therapy for OA in human beings and dogs is the NSAIDs, and the same probably is already true or is going to become true for cats. Because some of the pain of OA comes from prostaglandin release, NSAIDs alleviate pain and inflammation by inhibiting cyclooxygenase and reducing prostaglandin production. Some of the NSAIDs likely used in small animal practice have analgesic effects that are not attributable to cyclooxygenase activity. However, most of the NSAIDs used in small animal practice also inhibit proteoglycan synthesis and potentially worsen the pathology of OA.[25] Many NSAIDs also have undesirable gastric and renal effects so that management of OA with NSAIDs is a trade off between pain relief, potential deleterious cartilage effects, and gastric or renal side effects.

Inflammation, NSAIDs, and COX Inhibitors

Inflammation is caused by tissue damage and, among other things, causes pain. Damaged tissues release prostaglandins. Prostaglandins are 20-carbon organic acids that are potent triggers of pain, and are synthesized from unsaturated fatty acids such as arachidonic acid. Arachidonic acid is a 20-carbon unsaturated fatty acid produced by membrane phospholipids. Prostaglandins and leukotrienes are potent mediators of inflammation that are derived from arachidonic acid. The principal pathways of arachidonic acid metabolism are the 5-lipoxygenase pathway, which produces a collection of leukotrienes, and the cyclooxygenase pathway, which produces prostaglandin H_1 and H_2 (PGH_1, PGH_2). PGH_2 serves as the substrate for two enzymatic pathways: one leading to the production of several prostaglandins and the other leading to the production of thromboxanes (Figure 78-3).[26]

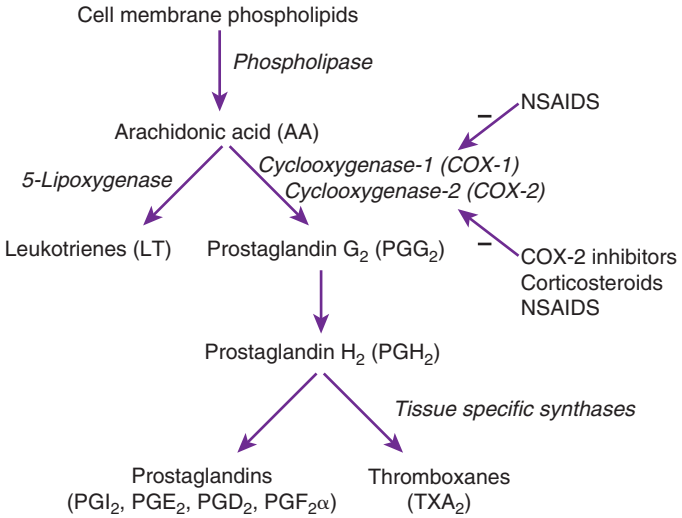


Figure 78-3. Schematic summary of the synthesis of inflammatory mediators from arachidonic acid, showing the inhibition of COX-1 and COX-2 by antiinflammatory drugs.

Two cyclooxygenase isoenzymes, COX-1 and COX-2, are known to catalyze the rate-limiting step of prostaglandin synthesis, and are the targets of NSAIDs. A third distinct COX isoenzyme, COX-3, has been described recently.[27] COX-1 is predominantly constitutive and is present in most tissues, particularly in platelets, the stomach, and kidneys. COX-1 is responsible for the production of prostaglandins important in physiological housekeeping functions that include normal vascular homeostasis and gastrointestinal protection. COX-2 is predominantly inducible, although it also has been found to be constitutive in the kidneys, brain, testicles, and tracheal epithelium of human beings. COX-2 expression and activity are induced by adverse stimuli such as inflammation and physiological imbalances and result in the production of inflammatory prostaglandins. COX-1 levels can increase by two to four times their normal values with inflammatory stimuli, while COX-2 levels can increase by 10 to 20 times.[26] COX-3 is expressed in several tissues, most abundantly in the cerebral cortex and heart. COX-3 appears to be inhibited selectively by analgesic/antipyretic drugs such as acetaminophen/paracetamol, phenacetin, antipyrine, and dipyrone. Inhibition of COX-3 may represent a primary central mechanism by which these drugs reduce pain and fever.[26]

NSAIDs achieve their effects by blocking the activity of cyclooxygenase. Inhibition of COX-1 may lead to gastric ulceration, gastrointestinal bleeding, and nephrotoxicity, whereas inhibition of COX-2 reduces pain and inflammation. Different drugs have varying abilities to inhibit the COX enzymes and this dictates their efficacy and side effects. The classical NSAIDs such as aspirin, ibuprofen, and naproxen inhibit COX-1 and COX-2 at normal doses. In addition to reducing the fever and pain of inflammation, classical NSAIDs also inhibit clotting (by interfering with the synthesis of thromboxane A_2 in platelets), and regular use results in a tendency to develop ulcers in the stomach and duodenum. Most NSAIDs inhibit COX-1 and COX-2. However, some newer drugs, the so-called selective COX-2 inhibitors, or coxibs, such as rofecoxib (Vioxx, withdrawn from the U.S. market in 2004) and celecoxib (Celebrex) are claimed to be much more active against COX-2 than COX-1, and that this makes them as effective as the classical, nonselective NSAIDs with better gastrointestinal tolerability in human beings.[43] However, the COX-1 and COX-2 story is not as simple as it was originally thought. The initial impression that COX-1 and COX-2 have unique and mutually exclusive functions now has progressed to a view that incorporates multiple complicated physiological pathways and functions. Both classical NSAIDs and COX-2 selective inhibitors exhibit a large range of relative potency for inhibiting COX-2 relative to COX-1.[27] The differing abilities of NSAIDs to inhibit COX-1 and COX-2 also appear to vary by species. What has been found to be true in human beings does not apply necessarily to dogs, and what has been found to be true in dogs does not apply necessarily to cats. Pharmacokinetic studies with NSAIDs and the so-called coxibs must be carried out in each species for which their use is being investigated.

Pharmacological methods have been used to develop assays that determine the degree of selectivity of a given NSAID for COX-1 and COX-2. Both in vitro and ex vivo methods of determining relative potency have been used to estimate the 50 per cent inhibitory concentration (IC50) of a variety of NSAIDs and coxibs in human beings. The IC50 values for each enzyme then are expressed as a ratio of COX-1 to COX-2 inhibition. The ratio for a COX-2 selective agent will be more than 1 because a more selective drug requires a lower concentration or IC50 to be effective.[28] In vitro methods rely on recombinant enzymes and are useful for screening drugs but are difficult to interpret and sometimes give contradictory results. Ex vivo assays that use whole blood now are widely accepted for the determination of COX selectivity in human beings. COX-1 activity is measured as thromboxane B_2 synthesis by platelets, whereas COX-2 activity is measured as PGE_2 synthesis in whole blood.[27-29] However, the biological assays cannot predict clinical outcomes unequivocally. Ex vivo assays identify COX inhibition at therapeutic plasma levels but not COX selectivity at tissue concentrations. The definition of COX-2 specificity serves to distinguish between compounds on pharmacological and not clinical grounds. Any benefit for COX-2 specificity needs to be established through randomized controlled clinical trials.

NSAID Treatment for Feline Osteoarthritis

No NSAIDs are licensed currently for long-term use in cats in North America or Europe. The only NSAID for which a safe chronic dose has been established is aspirin (10 to 20 mg/kg PO q48h).[3,30] Meloxicam probably is the most widely used drug for pain relief in cats in Canada and the United Kingdom, and it is gaining popularity in the United States since it has become available as a product licensed for use in dogs and cats. Meloxicam is available as a solution for injection with a strength of 5 mg/ml and as an oral suspension with a strength of 1.5 mg/ml in the United States, Canada, and the United Kingdom/Europe, marketed under the name Metacam (Boehringer-Ingelheim, Ridgefield, CT). The Canadian and UK/European dropper bottle delivers 0.1 mg/drop and the American bottle delivers 0.05 mg/drop. The Canadian bottle is meant to change to be like the United States.

Meloxicam is licensed for use in cats in Canada, the United Kingdom and Europe, and the United States only as a single subcutaneous injection for "the reduction of post-operative pain after ovariohysterectomy and minor soft tissue surgery,"

Table 78-3 | **Published Alternative Dosage Regimens for Meloxicam in Cats***

DOSE	DOSING FREQUENCY
0.3 mg/kg IV/SQ	Single administration only
0.1 mg/kg PO	q24h and limited to 4 days use
0.2 mg/kg SQ/PO	Initially, then
0.1 mg/kg PO	q24h for 2 days, then
0.025 mg/kg PO*	2-3 times per week

References 5,24,25,31-33.
*Certain references recommend up to 0.1 mg maximum dose per cat.[25,33]

according to the package insert. Even in dogs, for which meloxicam is licensed for "alleviation of inflammation and pain in both acute and chronic musculoskeletal disorders," the term "chronic use" has not been defined specifically on the package insert. The dosage regimens in Table 78-3 now have been published fairly widely, with the third regimen being intended for longer-term treatment of chronic conditions.[5,24,25,30-33] In spite of the fact that meloxicam is not licensed for use as anything other than a single dose, many practitioners are prescribing it currently. Cautious use of meloxicam without exceeding the currently recommended dosages, in the absence of concurrent conditions that would contraindicate its use (such as renal failure, gastrointestinal disease, or dehydration) and avoiding concurrent drugs whose use is contraindicated (such as furosemide or corticosteroids), appears to have been safe. Monitoring should include assessment of renal function and signs of gastrointestinal effects. However, the clinical efficacy of long-term pulse therapy with meloxicam remains to be determined.

As always with NSAID therapy, the clinician should use the lowest possible dose to minimize deleterious gastric, renal, and cartilage effects. Managing OA is a balancing act to maintain effective pain relief with minimal side effects and maximum owner satisfaction with treatment. Owner education is a vital part of this process. Practitioners should always remember to monitor for signs of gastrointestinal distress, renal dysfunction, or any other adverse effects while cats are on NSAID therapy. Ketoprofen (Ketofen, Merial, Duluth, GA) and tolfenamic acid (Tolfedine, Vetoquinol, Buckingham, UK) are licensed in Canada and Europe; however, neither drug is licensed for long-term use. Ketoprofen is licensed in Canada and Europe for the treatment of musculoskeletal and other painful disorders in cats for injectable use once a day for up to 3 days, or for up to 5 days orally, although some cats vomit when given ketoprofen. Tolfenamic acid is licensed in Canada and Europe as an antipyretic in cats for injectable use once and may be repeated once then given orally for 3 days. Carprofen (Rimadyl, Pfizer; Zenecarp, C-Vet, United Kingdom) is approved for use in Europe as a single perioperative injection in cats.

Corticosteroids and Analgesics

In addition to NSAIDs, corticosteroids and butorphanol also have been used to control pain in cats with OA. Corticosteroids are potent antiinflammatory agents that also decrease catabolic activity within the joints and reduce synovitis. However, corticosteroids also may damage articular cartilage with long-term use by decreasing the synthesis of collagen and matrix prostaglandins. Corticosteroids may be more deleterious to cartilage health than NSAIDs, and the clinician must realize that pain relief does not equate necessarily with chondroprotection.[3] Although butorphanol may cause sedation and corticosteroids may result in progression of degenerative changes, owners may be willing to tolerate these side effects if their cat's quality of life can be improved. As with NSAIDs, the clinical efficacy of long-term butorphanol therapy remains to be determined.

Chondroprotectants

Chondroprotectants, neutraceuticals, or slow-acting, disease-modifying osteoarthritic agents (SADMOA), given either by injection or as an oral nutritional supplement, also are available as an alternative or adjunct to other therapies. A brief review of these agents follows.* These compounds are believed to slow the progression of cartilage degradation and promote cartilage health by providing the necessary precursors to maintain and repair cartilage. Products containing SADMOAs are reported to have a positive effect on articular cartilage by enhancing hyaluronate production, inhibiting catabolic enzymes in osteoarthritic joints, and encouraging normalization of synovial fluid and cartilage matrix. Injectable chondroprotectants include polysulfated glycosaminoglycan (Adequan, Luitpold Pharmaceuticals, Shirley, NY), pentosan polysulfate (Cartrophen-Vet, Biopharm), and unsulfated glycosaminoglycan such as hyaluronic acid (sodium hyaluronate, Hyomate, Bayer, Germany). Adequan is licensed for use in dogs as is Cartrophen. Parenterally administered hyaluronic acid has been used in human beings and horses, but further studies are needed to document safety and efficacy in dogs. None of these products are licensed for use in cats.

Oral agents include glucosamine and chondroitin sulfate, which are available in several formulations for use in dogs and cats (Cosequin/Synoquin, Nutramax Laboratories, and Glycoflex, Vetriscience Laboratories).[35] Products containing a combination of glucosamine and chondroitin sulfate are the most common, and reports suggest that these two agents may act synergistically, possibly because of their postulated different mechanisms of action. Cortaflex (Horsham Nutraceuticals, United Kingdom) is a unique formulation of key refined, pharmaceutical grade isolates of chondroitin sulfate and glucosamine. These smaller molecules, glutamine, proline, glycine, glucuronic acid, and glutamic acid, are more likely to be absorbed than the larger molecules from which they are isolated. Once these key isolates are present in the joints, they are believed to trigger the body to produce its own natural chondroitin and glucosamine.

Glucosamine is an amino-monosaccharide precursor for the disaccharide unit of glycosaminoglycans, and it also is used directly by synovial cells in the production of hyaluronic acid. Sources of glucosamine include bovine trachea. Approximately 87 per cent of oral glucosamine is absorbed from the gastrointestinal tract.[31] Glucosamine normalizes cartilage metabolism and stimulates proteoglycan synthesis in vitro. Clinical trials in human beings have shown that glucosamine controls symptoms of OA and also improves cartilage health, joint motion, and radiographic signs of joint narrowing.[36-38]

Chondroitin sulfates are glycosaminoglycans found in hyaline cartilage. Chondroitin sulfate can be purified from

*A recent review paper presents the current state of knowledge in a detailed manner.[34]

bovine, whale, and shark cartilage sources, but because purified chondroitin sulfate is expensive, alternate sources of glycosaminoglycans have been sought such as extraction from *Perna* mussels (*Perna canaliculus*, the New Zealand green-lipped mussel). Approximately 70 per cent is absorbed after oral administration.[31] Glyco-Flex for cats contains pure freeze-dried *Perna canaliculus*. *Perna* contains all major classes of glycosaminoglycans including chondroitin-4-sulfate and chondroitin-6-sulfate, and also is rich in amino acids, naturally chelated minerals, numerous enzymes, vitamins, and nucleic acids. In vitro studies show that chondroitin sulfate increases proteoglycan synthesis, reduces collagenolytic activity, and inhibits degradative enzymes. Clinical trials in human beings show that chondroitin sulfate is effective in reducing the symptoms (pain and decreased joint mobility) of OA.[36,38] Studies using radiolabelled glucosamine and chondroitin sulfate show that both compounds are absorbed from the gastrointestinal tract and reach synovial fluid and articular cartilage in human beings and dogs to provide the necessary precursors for maintenance of cartilage health and, perhaps, even promotion of cartilage repair.[24,34,37,39] Anecdotal evidence and a limited number of clinical studies have shown that glucosamine and chondroitin sulfate are effective in treatment of OA.

Although recommending specific SADMOAs for the treatment of OA in cats is difficult, the best advice remains to use products that have been evaluated for safety and efficacy in well-designed experimental and clinical studies. Because glucosamine and chondroitin sulfate are available in various forms and grades of raw product, products should be used that have been manufactured using pharmaceutical industry standards.[34] Cosequin is one of the most purified sources of glucosamine hydrochloride and chondroitin sulfate, and it also contains manganese ascorbate. In vitro studies have shown that Cosequin may have a positive effect on joint health by promotion of glycosaminoglycan synthesis and suppression of proteolytic enzymes.[5,24] In vivo studies have shown that after cranial cruciate ligament injury, dogs treated with Cosequin had less OA.[31]

Other Nutritional Supplements

Other oral nutritional supplements include S-adenosyl-L-methionine (SAMe), omega-3 and omega-6 fatty acids, and antioxidants such as vitamins E and C, manganese, and selenium. SAMe is a molecule that normally is present in living cells and is involved in several anabolic and catabolic reactions. As a precursor of polyamines, SAMe has antiinflammatory, analgesic, and free radical scavenging properties. Polyamines also are involved in cell proliferation, protein synthesis, and stabilization of prostaglandins to protect them from enzymatic destruction.[5] SAMe is available as an oral product, Denosyl SD4 (Nutramax, Edgewood, MD), for the treatment of liver disease in dogs and cats and is metabolized into homocysteine, then cysteine and glutathione. The use of a balance of essential fatty acids and antioxidants suffers from a lack of controlled studies to document efficacy in treating joint disease, although these compounds may be added to some pet food diets or supplements.[34,39] Ascorbic acid, for example, is present in Cosequin. Many of these agents have been used in treatment of OA in animals despite the lack of definitive clinical trials confirming their efficacy. Botanicals such as the yucca and turmeric plants also have been proposed as potentially chondroprotective, but further research is needed to standardize the plant extracts before controlled studies on safety and efficacy can be performed.[39]

POSTTREATMENT ASSESSMENT

The goal of treatment is alleviation of pain and return to normal behavior or preservation of function. With successful treatment of the pain and discomfort of OA, one would expect to see a return to having a good appetite, a general appearance of well-being and enjoying normal activities, including eating, stretching, grooming, and playing.

SUMMARY

The diagnosis of OA requires an index of suspicion, especially in older cats. Practitioners should consider the use of a client questionnaire, particularly for examinations of old cats. Therapy for OA should be based on good clinical evidence of efficacy. The results of controlled clinical trials must be appraised critically.[40-45] Much more research on OA is needed in cats, with clarification of the frequency, causes, and treatment. As mentioned at the beginning of this chapter, several retrospective studies have now been completed. What is needed now are prospective studies and randomized blinded clinical trials of therapy for OA. In 2003, the University of Glasgow initiated a prospective study of OA in cats. Preliminary findings of this study suggest that most cats with pain and OA showed behavioral and/or lifestyle changes such as a reluctance to jump, reduced grooming, and inactivity.[46] The Animal Health Trust, in collaboration with the United Kingdom's Feline Advisory Bureau, initiated a prospective study in 2004 to determine the prevalence of, and risk factors for, OA in first opinion and referral practices in the United Kingdom. We can look forward to the findings of these studies sometime in the near future.

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