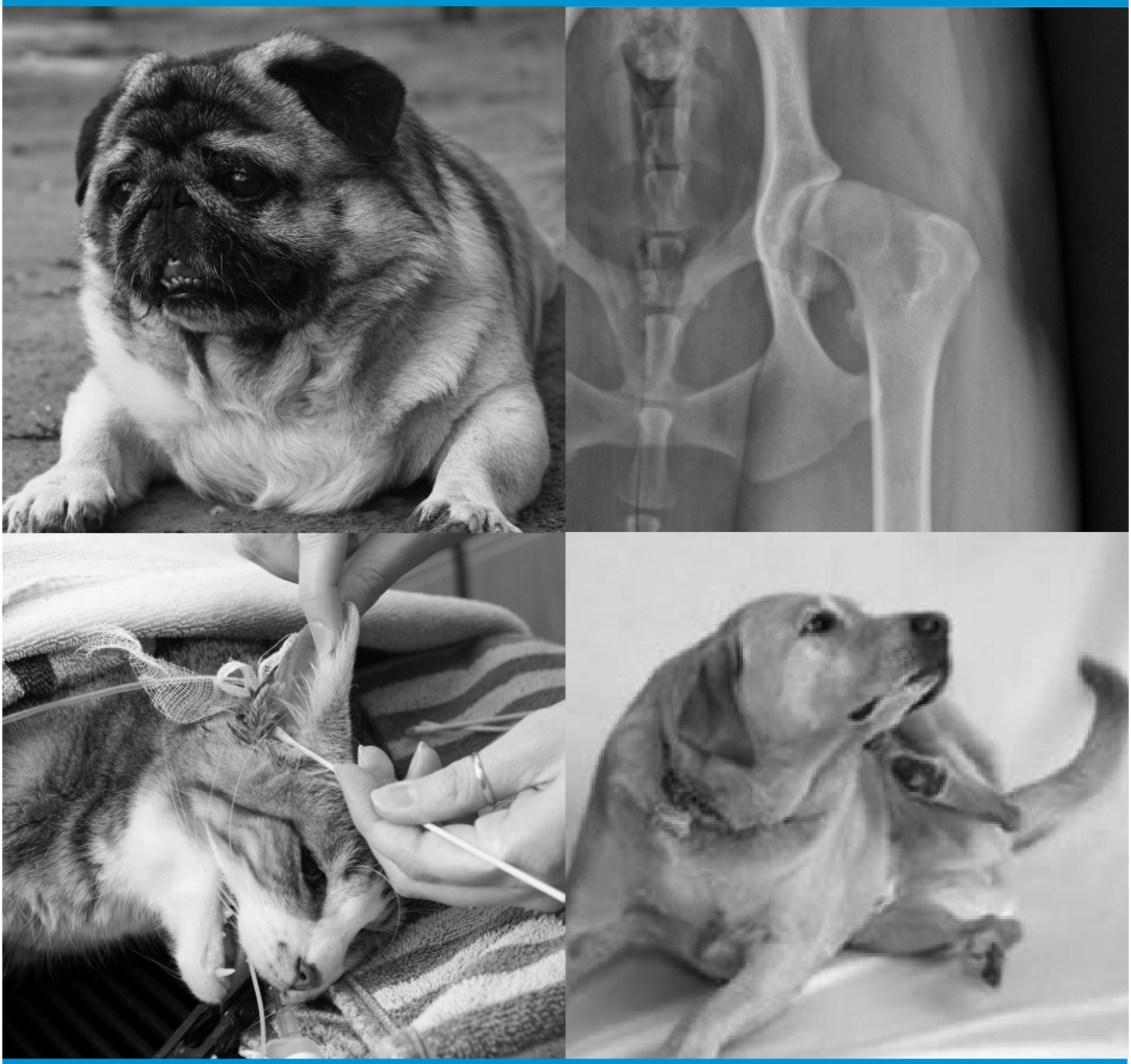
2012 PROCEEDINGS



Insights from the Experts

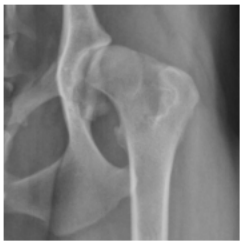
Pfizer Advanced Learning Series

Pfizer Animal Health

INSIGHTS FROM THE EXPERTS

2012 PROCEEDINGS



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Pfizer Advanced Learning Series

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New Thoughts on Atopic Dermatitis and Treating Itchy Dogs

Douglas J. DeBoer, DVM, Diplomate, ACVD; Valerie Fadok, DVM, PhD, Diplomate, ACVD

ABSTRACT

Canine atopic dermatitis (AD) is a multifaceted disease that presents with the hallmark sign of itching. Research continually reveals new aspects of allergic skin disease, from elements of its pathogenesis and improvements in diagnostic criteria, to more effective and safer treatments. Understanding these new findings is the key to improving our approach to the diagnosis and clinical management of AD and other pruritic conditions. As our scientific understanding of AD evolves, treatment approaches are being developed that specifically target these newly identified abnormalities in pathobiology in atopy patients.

POINTS TO PUT A FINGER ON

- Atopic dermatitis (AD) has complex pathobiology and recent research has informed a new view of the processes involved. These findings have the potential to inform the development of several new treatment approaches for AD.

- There is no accurate test to diagnose AD. The diagnosis is made clinically by clinical signs and excluding other causes of itching.

- Current treatment regimens for AD focus on addressing multiple aspects of the disease pathogenesis:
  - Abnormalities in the epidermal barrier
  - Environmental exposure to potential allergens
  - Controlling concurrent infections or colonization with common pathogens, such as *Staphylococcus pseudintermedius* or *Malassezia yeast*
  - Controlling the immune responses to allergenic stimulation
  - Controlling stimulation of the itch response

- Therapy for AD is typically aimed at both the primary disease as well as the secondary complications. Many atopic patients require lifelong management with multimodal regimens that are individualized to their specific needs, so it is important to consider long-term safety as well as convenience and the cost-effectiveness of treatment regimens.

- Decreasing pruritus remains a key therapeutic objective for veterinarians treating atopic dogs, possibly driven by the need to address the owner's complaints that persistent itching and scratching in their dog is detrimental for the pet and disrupts quality of life for both pet and owner.

- Contemporary, multimodal treatment protocols can include one or more of the following therapeutics based on individual patient needs:
  - Nutritional supplements or topical therapies to reduce barrier permeability and enhance barrier function
  - Altering the environment to minimize exposure to allergens
  - Anti-infective drugs to treat secondary infection
  - Hypoallergenic diets

- Antipruritic therapy to control itch and scratching
- Allergen-specific immunotherapy to decrease the patient's immune response to specific allergens
- Managing inflammation by moderating the animal's immune response using drugs, such as cyclosporine

☛ Future options for treating AD may include drugs that are targeted at controlling recently described mechanisms of AD such as specific cytokines. IL-31 is a key focus in many of these investigations.

☛ In a validated questionnaire, AD was been shown to have a significant impact on eating, activity, behavior (particularly with regard to treatment), and sleep in canine patients. The higher the pruritus score, the lower the quality of life. It may be worthwhile to incorporate quality-of-life assessments as part of the evaluation for success of treatment.

PATHOGENESIS OF ATOPIC DERMATITIS: NEW FINDINGS, NEW TREATMENTS

The pathogenesis of AD is complex and incompletely understood, even in humans. Modern research efforts are providing new insights into our understanding of the pathobiology AD. This research is permitting the identification of new therapeutic targets that could lead to the development of innovative therapeutic options for AD in the future.

Atopic Dermatitis—Inside–Outside?

Early views of AD characterized it as an "inside-outside" process. The disease was thought to begin on the "inside" of the individual patient—in the immune system. "Outside" influences, such as allergens, irritants, bacteria, and yeast, were believed to cause development and worsening of symptoms. AD was considered to be an IgE-mediated, immediate-type (type I) hypersensitivity response to inhaled allergens; thus it was referred to as "allergic inhalant dermatitis" In this view of AD, the IgE produced would bind to cutaneous mast cells. Upon reexposure the allergen would bind to and cross-link surface bound allergen-specific IgE molecules. The mast cells would then degranulate, with subsequent release of mediators that caused the clinical signs and itching.

Atopic Dermatitis—Outside–Inside?

More recently, this "inside–outside" view has been called into question, and a different view is evolving. It began with the observation that many of the factors associated with AD involved both the epidermis itself and other "outside" influences. Perhaps AD may begin first as a defect in the "outside" —for example, in the epidermal barrier? As a result of this defective barrier, the immune response was altered, triggering the inflammatory cascade.

Epidermal Barrier Function in Atopic Dermatitis

Because many of the abnormalities recently identified in patients with AD involve some aspect of the epidermal barrier, it is useful to examine this concept more closely. The epidermal layer of the skin functions as the initial barrier to antigens that can initiate an atopic or allergic reaction. The skin barrier is comprised of cornified cells in the stratum corneum and planar sheets of lipid between them (1, 2). The stratum corneum provides a permeable barrier preventing excessive water loss and an antimicrobial barrier preventing the penetration of pathogens while allowing colonization of the skin surface by "friendly" bacteria. The lipid of the stratum corneum contains enzymes that break down lipids and proteins in the corneodesmosomes, facilitating invisible desquamation. It also contains antimicrobial peptides that act as natural antibiotics to help prevent infection.

A crude assessment of barrier function in the skin of dogs and humans is measurement of transepidermal water loss (3, 4). Another way to assess the barrier is by transmission electron microscopy. The stratum corneum from atopic patients reveals disorganized lipid between the corneocytes and retention of lamellar bodies, suggesting that part of the abnormality is associated with reduced lipid.

We are slowly accumulating evidence that a barrier defect may contribute to the pathogenesis of AD in dogs (5, 6). Marsella and colleagues recently reviewed the evidence in *Veterinary Dermatology* on behalf of the International Task

Force on Canine AD. Preliminary evidence indicates that atopic dogs may have increased transepidermal water loss and decreased ceramides in the stratum corneum. Ultrastructural studies have shown that dogs with AD have abnormal and disorganized lipids in their stratum corneum compared with normal dogs (7, 8). At least two studies have found decreased ceramide levels in the skin of atopic dogs compared with those in normal dogs (9, 10). The evidence for abnormal filaggrin is less reliable. A laboratory model of canine AD exists: the high IgE-producing beagle. Some but not all of these dogs have abnormalities in distribution and expression of filaggrin when compared with normal beagles. By contrast, filaggrin does not seem abnormal in atopic West Highland White Terriers when compared with normal ones.

Barrier dysfunction is complicated: causal factors can be primary, as described above, or secondary. Many of the bacteria and yeast that infect the skin of atopic dogs could contribute to barrier breakdown. It was shown recently that proteolytically active allergens can also cause barrier breakdown (11).

Immunopathogenesis of Allergy: New Targets for Control of Itching

Great strides have been made in our understanding of AD in human beings, and much of what has been learned for people can be applied to dogs until we can verify that similar mechanisms exist (2, 12).

Understanding the immunopathogenesis of AD may require a refresher course in immunology. Two major teams fight our immunologic battles: the innate immune system and the adaptive immune system. The innate immune system consists of white blood cells, such as the neutrophil, the macrophage, and the natural killer cell, along with assists by epithelial cells. There are natural antibodies; the complement system; the coagulation system; and the natural peptides, such as the defensins. These are ready to go at any time, but their response is not specific and they have no memory. By contrast, the adaptive immune system provides specific cellular and humoral support (antibodies) has long-term memory. This immune system includes the T lymphocytes, which provide support for killing viruses, fungi, and intracellular organisms, as well as the B lymphocytes, which make antibodies. There are two major types of T-helper lymphocytes: T helper 1 (Th1) cells, which help to mount a cellular immune response, and T helper 2 (Th2) cells, which support antibody production. Each set produces a different cassette of cytokines that facilitate their function.

The immune reaction in AD involves an antigen presenting cell (Langerhans cell) which presents an antigen to a naive T cell and instructs it on the correct response. It may be "directed" to produce cytokines that classify it as a Th1 cell. These cytokines are produced primarily to kill intracellular pathogens and/or provide help to white blood cells to kill extracellular pathogens. The immune dysregulation in allergy is a shift toward a Th2 response. This response promotes the T cell to make the type of cytokines and mediators that make eosinophilic inflammation and overproduce allergen-specific IgE. IgE is the only antibody that binds to its receptor on mast cells and other cells without binding to the allergen first. When the allergen is absorbed into the skin (increased perhaps because of abnormal skin barrier function) it cross-links two allergen-specific surface-bound IgE antibodies, triggering mast cell release. However, a plethora of other inflammatory reactions also occur because of the type of cytokines produced by these allergic T cells.

It has been shown experimentally that AD can be induced in mice devoid of IgE. Thus, while the presence of allergen-specific IgE appears to make the symptoms of AD worse, it is not required for the disease to occur. Atopic patients develop disease because they are genetically predisposed; they have a variety of genetic polymorphisms that increase production of certain cytokines and lower production of others. Some experts have theorized that that the presence of IgE is merely an "epiphenomenon" or marker of the true underlying disorder. In humans, about 70%–80% of patients with AD have demonstrable allergen-specific IgE in serum or are positive on "allergy tests"; 20%–30% do not and are not positive on these tests. In absence of being able to routinely document this "inside" abnormality in all patients with AD it seemed reasonable that other mechanisms may be involved.

A popular but controversial and imperfect hypothesis for the increase in atopic diseases in developed countries is the hygiene hypothesis (13). The hypothesis states that hygiene has improved to an extent we are exposed to lower levels of endotoxins and other stimulators of the innate immune response. Endotoxins are derived from the cell walls of gram-negative bacteria. This results in an imbalance in the way our immune systems develop, with a skewing toward

the allergic response. We don't know much about its role in veterinary medicine; however, a preliminary but intriguing study recently showed an inverse correlation between the levels of endotoxin in the coats of Labrador retrievers and their incidence of AD (14).

A key factor that mediates the pruritus of AD is the release of a variety of cytokines, lipid mediators and enzymes (including proteases) during the allergic response. These bind to their various receptors to induce the inflammatory response. Some of these receptors are present on nerves. A cytokine called IL-31 (15–17), produced by Th2 cells, is a popular candidate for inducing pruritus and is currently being targeted for new therapies.

Neurologic stimulation is also part of the atopic disease process. Itching is mediated by free nerve endings that penetrate into the epidermis and dermoepidermal junction (18). Because inflamed keratinocytes can produce nerve growth factor, the actual number of nerve fibers can increase over time, lowering the threshold to start the pruritus. Substance P is also produced in excess in patients with AD and it contributes to the increase in nerve fibers as well as mediating pruritus via the NK-1 receptors. Lastly, when steroids, immunotherapy, and cyclosporine fail, many veterinary dermatologists use gabapentin at an initial dose of 11–15 mg/kg TID. This drug can be very sedating and may need to be reduced to BID dosing. Its mechanism of action is not clear, but it is suspected to inhibit the transmission of pruritus signals through the spinal cord (19). Like cyclosporine, this drug may take several weeks to be fully effective.

Additionally other mechanisms were shown to be important in human AD. These included: (1) a defect in the epidermal barrier function which could result in higher permeability of the skin to allergens and irritants; (2) reduced production of antimicrobial peptides by epidermal cells, leading to greater propensity for skin infections; (3) augmentation of the inflammatory response by substances secreted by microorganisms on the skin, such as staphylococcal exotoxins; (4) identification of genetic polymorphisms highly associated with AD and allergy, some of which involved genes coding for structural proteins of the epidermis or elements of the inflammatory cascade; and (5) recognition that environmental conditions can affect or modify development of the allergic response in a genetically predisposed individual (the "hygiene hypothesis"). Subsequently these came under investigation in animal allergy. For clinicians, the possibility that that multiple mechanisms may be contributing to the atopic disease in a given patient can makes the diagnosis and treatment of AD complex and potentially difficult to manage.

Implications for Treatment

Given the complexity of the pathogenesis of AD, the goal of treatment is to find the precise combination of therapeutic approaches that effectively provides relief for each individual patient. Multimodal treatment modalities aimed at both the primary disease and at secondary complications can be required. And since many atopic patients require lifelong management it is also important to consider long-term safety as well as convenience and the cost-effectiveness of treatment regimens.

Classically the goal of therapeutic regimens for AD was focused on managing inflammation. Today treatment strategies must address multiple elements:

- Augment the permeability of the skin barrier to reduce entry of allergens and irritants
- Avoid or eliminate allergens where possible
- Augment the antimicrobial barrier to reduce the frequency of secondary infections
- Control secondary infections, commonly due to *Staphylococcus pseudintermedius* or *Malassezia* yeast, which contribute to discomfort and augment the allergic and inflammatory responses
- Manage itch and control scratching that can perpetuate skin damage
- Modify the immunologic response through allergen-specific immunotherapy

- Manage the remaining inflammatory responses that persists despite the above measures

Successful implementation of therapy requires client education about AD and the treatment goals. "Reactive therapies" including corticosteroids and other anti-inflammatory drugs can be useful in the short-term to get a rapid decrease in clinical signs. But other approaches, such as repair of barrier function and modification of the immune response, are "proactive treatments" aimed at correcting the underlying pathogenesis of the disease and effect improvement over a more prolonged period. Owners must be educated that this "preventive approach" can be the best chance of controlling this lifelong disease with minimal use of drugs that may be detrimental over the long term.

APPLYING NEW INSIGHTS TO TREATMENT STRATEGIES

New facts about AD have resulted in important changes in our thinking about how the disease works in dogs and form the basis of what could be exciting new approaches to treatment in the future.

What can we do for barrier repair in dogs? Several types of products are currently available. While few evidence-based studies to support their efficacy exist, anecdotal and clinical experience has been positive in some patients.

- Phytosphingosine-containing products are available as shampoos, sprays, ear washes, gels, and lipid spot-on formulations (Douxo product line, Sogeval). In the clinical experience of the authors (Fadok), regular use of these products were noted to reduce the recurrence of staphylococcal pyoderma but to have little effect on pruritus. Additionally we have the clinical impression that these products may be better for treatment of hyperkeratotic states and those associated with comedones.

- Dermoscent Essential 6 is an oil product made from the extract of several herbs. Evidence proving efficacy is lacking. Tretter and Mueller recently reported that Dermoscent had some efficacy in the treatment of canine AD by reducing transepidermal water loss, as well as pruritus and the CADESI score used to quantify lesions in atopic dogs (20).

- Allerderm Spot-on (Virbac) is a product that contains ceramides, which restores ceramide levels toward normal and improve the structure of the lipid bilayers between corneocytes (21). A preliminary study suggests some clinical efficacy in the treatment of canine AD (22).The hypothesis is that continued use of this type of product over time helps the skin repair itself, thereby reducing entry of allergenic and microbial proteins. In the experience of the author (Fadok) some dogs with AD and recurrent pyoderma have responded to treatment with Allerderm Spot-on. The most dramatic improvement noted was in dogs with dry coats, especially Labrador retrievers. A number of these patients appeared to have a decrease in recurrence of staphylococcal pyoderma, but no decrease in itching was observed in severely atopic dogs.

- Diets that include supplemental fatty acids may also improve barrier function. Studies definitively show that feeding diets enriched in fatty acids can improve the organization of lipids in the stratum corneum of atopic dogs (26).

Staphylococci and Allergic Skin Disease

It is clear that there is a special relationship between allergic skin disease and staphylococcal colonization or infection. Allergic patients of many species—especially human beings and dogs—are prone to recurrent "staph infections." These infections not only cause discomfort they may also augment the allergic response, creating a kind of positive feedback loop. Thus, treatment *and prevention* of recurrent infection are the cornerstones of a therapy plan for allergic patients.

The recent emergence of multidrug resistant staphylococcal strains has been reported from many areas of the world. In some locations, 30% or more of strains cultured are methicillin-resistant. These strains include *pseudintermedius*, *aureus*, and *schleiferi* species. Methicillin-resistant staphylococci (MRS) are of particular concern.

The emergence of these strains has several clinical implications:

1. If you treat a dog with *Staphylococcus* pyoderma with a beta-lactam antibiotic (cephalosporin or augmented penicillin) and there is no response, culture and susceptibility testing is now *mandatory*, because it is impossible to

accurately predict the susceptibility pattern of a resistant organism.

2. If you do identify an MRS organism, especially if it seems to be very resistant, order *Staphylococcus* speciation. If the organism turns out to be highly methicillin-resistant human-origin *S. aureus* (MRSA), the owners should be notified so that they can discuss the situation with their own health care provider. The patient is a potential human health hazard and should be treated as such until the infection is fully cleared.

3. We must redouble our efforts to use antibiotics wisely and judiciously and reconsider all efforts to use alternate nonantibiotics to treat recurrent infections whenever possible.

Implications for Treatment

In some cases systemic antimicrobial therapy is needed to get the bacterial colonization under control so that topical therapy can be used to manage recurrences. There is a strongly emerging view that we must use antibiotics appropriately, limiting their use to confirmed, active infections, and looking for alternative treatments and preventive measures in animal with recurrent infection. These include topical therapy with active ingredients such as:

- Chlorhexidine spray or shampoo—Dogs with mild, superficial infections often can be treated very effectively with daily topical treatment with 2%–4% chlorhexidine spray or shampoo, without systemic antibiotics. To prevent recurrence, shampoos containing chlorhexidine, benzoyl peroxide, or phytosphingosine seem to be especially helpful when used twice weekly and allowed to remain on the pet for 5–10 minutes before rinsing. Any product formulated to remain on the skin or that has prolonged antimicrobial action is preferred for these cases.

- Spray-on or "leave-on" conditioner products containing chlorhexidine and/or phytosphingosine—Cases with broader regions of the skin effected. Recently, products containing saccharide molecules that interfere with attachment of bacteria and yeast to the skin ("glycotechnology") have become available and may be beneficial for limiting colonization. In addition, sprays or wipes containing nisin (an antiseptic used in dairy teat dips) or hypochlorite ion (dilute bleach solutions or similar products) have recently become very popular. The overall principle here is to limit, to the extent possible, prolonged or repeated courses of antibiotic treatments to minimize the potential for selection of resistant bacteria.

- Mupirocin ointment (2%)—For localized areas, daily treatment with 2% mupirocin ointment is highly effective and precludes the need for systemic antibiotics.

Controlling Itching

The complexity of the soluble mediators produced by the immune system may explain why there is a poor response to treatment with antihistamines. Antihistamines primarily aimed at H1- and H2-receptors are the most common choice in veterinary medicine. New experimental evidence suggests that targeting H4-receptors may be worthwhile because this receptor is expressed on T lymphocytes, antigen presenting cells (Langerhans cells) and keratinocytes (24–27).

The drive to better understand the specific mechanisms mediating AD is to develop new targets for treatment, particularly those that will control pruritus. The mainstay for allergy management over the years has been the use of glucocorticoids. These are wonderful drugs that have global anti-inflammatory activity; however, the risks for side effects are real and need to be considered. The problem with using glucocorticoids as monotherapy for AD is the development of resistance over time, requiring higher doses and more frequent use, increasing the risk for significant side effects. The side effects associated with glucocorticoids tend to be more severe when high doses are used for long periods; however, it is critical to understand that individual variation is great, and some dogs can develop considerable side effects at low doses. The most common side effects are weight gain and polyuria with polydipsia, but we can also see drying of the skin and coat, with increased risk for secondary bacterial infections in the skin. Even low-dose steroids can predispose dogs to urinary tract infections, and it is advised that dogs taking steroids for allergy management have urine cultures done once or twice yearly to check for occult infection. We can also see significant behavior changes; increased serum alkaline phosphatase and sometimes alanine transferase; thinning of the coat; thinning of the skin with

prominent vasculature; comedone formation; and in extreme circumstances, calcinosis cutis. Muscle wasting and loss of bone density are also possible.

While steroids can cause significant problems, the drugs have been demonized unfairly. It is important to realize that steroids or other antipruritic therapy may be necessary, at least in the short term, to quickly relieve scratching and prevent self-trauma. Some dogs will require long-term steroids as well. Sousa has developed a very useful formula to calculate a "safe steroid dose" if long-term use is required. This dose is based on what a dog would produce endogenously per year, and proposes a means to help minimize risk for significant side effects, such as iatrogenic Cushing's Disease or calcinosis cutis. The dose is based on body weight: Body weight (in kg) is multiplied by 30, and the resulting number gives the maximum annual dose of prednisone or prednisolone the dog can be given with minimal risk for side effects. So for example, a 10-kg dog could take approximately 300 mg prednisone or prednisolone per year. This is quite a low dose, and for that reason, many of us recommend Temaril-P. This product contains an antihistamine trimeprazine with 2 mg prednisolone per tablet. The 10-kg dog could therefore take 150 Temaril-P per year, or roughly 1 tablet every other day. If that controls the pruritus, then that is a reasonable therapeutic path. But because low-dose steroids cannot control pruritus in severe cases and high-dose steroids have significant side effects, we are eager to look for other means to reduce pruritus, including targeted therapies that are currently being investigated. This requires an understanding of the mechanisms that mediate this complicated disease and may necessitate a flash refresher course in immunology.

Cyclosporine, tacrolimus, and pimecrolimus (used in children) are calcineurin inhibitors that suppress the inflammatory cytokines produced by T lymphocytes. Because these cytokines are upstream of the actual itch event and because they are not the only mediators of disease and pruritus, these medications can take several weeks to be fully effective. However, topical calcineurin inhibitors have been shown to exacerbate skin barrier dysfunction (28).

Lastly, new drugs that target specific cytokines with monoclonal antibodies and drugs that target their signal transduction mechanisms has been effective in many models and may lead to effective and safe therapies in the future.

Allergy Testing and Immunotherapy

The use of a confirmatory "allergy test" is commonly considered in the diagnosis of AD. The first and most important thing to understand about "allergy testing" is that *no allergy test is perfect*. Allergy tests of different types have varying sensitivities and specificities, and all types have (to a greater or lesser extent) "false negatives" and "false positives." Therefore, allergy tests do not answer the question, "Is this pruritic patient allergic?", because some patients with other pruritic diseases will also be positive. A striking example is in canine scabies, where the presence of the scabies mite evokes an allergic response that may cross-react with other mites. Dogs with scabies can be highly positive on an allergy test to house dust mites, which could obviously lead to a rather serious error in diagnosis and treatment. Rather, allergy tests answer the question "in this patient for which I have already made a *FIRM* clinical diagnosis of AD, to which substances is he/she allergic?"

Why and When to Allergy Test

The major reason to perform an allergy test of any type is not to diagnose the disease. Why, then, consider allergy testing? *To allow the clinician to select allergens for use in allergen-specific immunotherapy…period!* Identifying the specific allergens to which a patient is sensitive may also enable the owner to pay closer attention to environmental factors that contribute to allergen exposure. However, the owner should probably be warned that the results of the test rarely reveal an allergy to something that can be readily removed from the pet's environment.

When should you allergy test? Again, the first answer is "after you have already diagnosed allergy." That aside, results of allergy testing can vary throughout the seasons. This is not true with every dog, in every situation. However if you have to choose a time to allergy test, the best time would be just after the pet has been exposed to every pollen and dust allergen for that season. In cold-weather areas, this means that allergy testing is best done in the late summer to fall, just after all pollination cycles are complete. In this case, the allergic response will be maximally "cranked up" to as

many allergens as possible. As an example, a pollen-allergic pet may be highly symptomatic in May. But in May, it's been 10–11 months since its immune system has been exposed to June and July pollens…so theoretically it's a suboptimum time to test. However, these principles are in part theoretical and will vary with climate and with individual pet. The age of the pet may also influence the decision to test.

Which Test Is Best?

It is useful to examine the different principles on which allergy tests rely. Intradermal testing (IDT) is the method of choice for many specialists in veterinary dermatology and allergy. IDT has the advantage of being a biological method that in some ways mimics the pathogenic mechanism of the actual disease. Positive IDT requires not only the presence of specific IgE antibody, but functional mast cells and microvascular response. With the notable exception of house dust mite allergen, nonallergic dogs seldom yield false-positive results on IDT. It is also considered by some authorities to be more sensitive than serum-based methods. However, there are important drawbacks to IDT, the most obvious of which are its requirement for referral and for discontinuation of treatment for weeks to months before testing. Being dependent on a biological system, results of IDT are subject to multiple other influences such as stress, concurrent disease, and presence of inflammatory skin lesions. IDT also occasionally yields negative results in some animals with strong clinical signs of AD.

In vitro testing methods (serum-based tests) are increasingly being used both by specialists in veterinary allergy and by general practitioners. When done reliably and used properly, these tests are very valuable for formulating an immunotherapy prescription. These are "IgE tests"—they measure only the amount of allergen-specific IgE present in the serum, not whether the IgE is causing an allergic reaction. These tests do not prove cause and effect. In using serum-based tests, we assume that if allergen-specific IgE is present it is capable of causing allergic signs, but this is not necessarily true! As is now hopefully clear, it is certain that *there's more to allergy than just IgE.*

Generally, serum allergy testing is convenient and accessible, but in some cases seems to lack specificity: With this test, the big problem may be "false-positive" results. Some people call these "clinically insignificant true positives" because the animal may have serum IgE against one or more allergens but without clinical significance. One strong advantage of the serum allergy tests are that they are unaffected, or at least less affected, by therapy. Antihistamine treatment will render an IDT completely negative but it has no effect on serum tests. With regard to corticosteroids, several laboratories recommend withdrawal of therapy for a period before serum testing. We believe that there is no clear evidence that use of medications, such as corticosteroids, meaningfully affects serum test results. Although these serum-based methods have much to offer—especially when referral to a specialist is not possible—they must be used and interpreted cautiously.

In general, studies have concluded that all serum-based methodologies (and, indeed IDT as well) are very poor choices for diagnosing food allergy. They are not sensitive or specific even in humans. Part of the explanation is that food allergy does not always involve IgE-mediated processes. Therefore, even if we did have a perfect "IgE test" for food allergens, it would still be inaccurate for use in diagnosing food allergy. Some authorities believe that these tests do have some value in helping to select the best diet to be used in a dietary restriction–provocation trial, which is the only test that should be used for food allergy.

Implications for Treatment

Allergy testing is used as a prelude to one of the most valuable, and possibly most underused, specific allergy treatment methods—allergen-specific immunotherapy (ASIT), or "allergy shots." Allergen-specific immunotherapy is a treatment for AD in dogs and cats wherein extracts of allergens to which the patient is sensitive are injected, in gradually increasing amounts, to lessen or reverse the hypersensitivity state. It is the *only* treatment we have that can directly reverse part of the underlying pathogenesis of the disease, and it can do this at reasonable cost, with success in most animals, mostly without adverse effects, and for the animal's lifetime. Chief disadvantages include that it takes several months or more to begin working and that it is not always effective.

Most effects of ASIT are believed to be allergen-specific rather than nonspecific. Thus, accurate testing to identify the offending allergens in each patient is of paramount importance to successful immunotherapy. In particular, the clinician must strive to avoid false-positive allergy test results, which would result in including an allergen in the patient's mixture that is not relevant to that individual's disease.

The exact protocol and schedule for injections varies according to the allergen preparation; generally, the extract manufacturer will provide an appropriate schedule. Injections are given year-round, and the minimum initial trial period should be 12 months. As far as is known, concurrent treatments with antihistamines, fatty acid supplements, cyclosporine, or low-dose glucocorticoids will not interfere with response. Treatment is generally considered to be life long, although discontinuation after 2–3 years of injections if the animal has responded very well can be attempted. Expected response rate to immunotherapy is approximately 60%–70%, of dogs achieving a "good-to-excellent" response (defined as at least 50% improvement in clinical signs). Response can be seen as soon as 1 month, but more typically takes 3–6 months to occur, and the maximum response may take at least 1 year. Adverse reactions to allergen immunotherapy include localized itching at the injection site and transient worsening for 12–24 hours after the injection (in about 10% of patients). Generalized anaphylaxis occurs in less than 1% of dogs and cats; such reactions are generally mild, and further reaction can usually be prevented by pretreatment with oral antihistamines 1–2 hours before each injection.

QUALITY-OF-LIFE ISSUES IN ALLERGY

Any veterinarian who sees atopic dogs has listened to the frustrations of the owners in dealing with the pruritus, the odor, the hair loss, and the never-ending nature of this disease. Often these dogs end up marginalized within the home or surrendered to shelters. Many owners who have no experience themselves with allergies have unrealistic expectations about what can be achieved. It is critical to help them understand that allergies are forever. We control these diseases, we do not cure them. Atopic dogs are high-maintenance forever, and they will probably always itch more than normal dogs. This reality is hard for people to accept, but to be successful in allergy management we need to be content with small changes that occur over long periods. It is critical to see these patients regularly, to invest in the concept of multimodal management of the disease (as suggested in the guidelines from the International Task Force on Canine Atopic Dermatitis [29]), and to be creative when therapies fail or become ineffective over time.

We are just beginning to assess quality-of-life issues for dogs and their families (30–32). Noli and colleagues have developed a validated questionnaire to determine these effects (31, 32). For dogs, the disease had significant impact on eating, on activity, on behavior (particularly with regard to treatment), and their sleep. For the owners, mental and physical fatigue, financial stress, and time devoted to treatment were major factors. It should come as no surprise to any of us that the most frustrating problem is pruritus, and the higher the dogs scored on pruritus the lower the quality of life. Although not statistically significant, there was improvement in quality of life for pet and owner when pruritus was reduced, except for the burden of treatment. It may be worthwhile to incorporate quality-of-life assessments as part of our evaluation for success of treatment. The more we can help the client understand the disease (and of course, the more we can control pruritus), the more we can reduce the effects on the family's quality of life. There is a lot of support that clients need when they are managing an atopic dog. It behooves each of us to own one of these dogs so we understand the impact of what we ask our clients to do.

REFERENCES

1. Elias PM, Schmuth M. Abnormal skin barrier in the etiopathogenesis of atopic dermatitis. Curr Allergy Asthma Rep. 2009;9:265-72.

2. Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. Immunol Rev. 2011;242:233-46.

3. Cornegliani L, Vercelli A, Sala E, Marsella R. Transepidermal water loss in healthy and atopic dogs, treated and untreated: a comparative preliminary study. Vet Dermatol. 2011.

4. Lau-Gillard PJ, Hill PB, Chesney CJ, Budleigh C, Immonen A. Evaluation of a hand-held evaporimeter (VapoMeter) for the measurement of transepidermal water loss in healthy dogs. Vet Dermatol. 2010;21:136-45.

5. Marsella R, Olivry T, Carlotti DN; International Task Force on Canine Atopic Dermatitis. Current evidence of skin barrier dysfunction in human and canine atopic dermatitis. Vet Dermatol. 2011;22:239-48.

6. Olivry T. Is the skin barrier abnormal in dogs with atopic dermatitis? Vet Immunol Immunopathol. 2011.

7. Inman AO, Olivry T, Dunston SM, Monteiro-Riviere NA, Gatto H. Electron microscopic observations of stratum corneum intercellular lipids in normal and atopic dogs. Vet Pathol. 2001;38:720-3.

8. Marsella R, Samuelson D, Doerr K. Transmission electron microscopy studies in an experimental model of canine atopic dermatitis. Vet Dermatol. 2010;21:81-8.

9. Reiter LV, Torres SM, Wertz PW. Characterization and quantification of ceramides in the nonlesional skin of canine patients with atopic dermatitis compared with controls. Vet Dermatol. 2009;20:260-6.

10. Ishikawa J, Narita H, Kondo N, et al. Changes in the ceramide profile of atopic dermatitis patients [Letter]. J Invest Dermatol. 2010;130:2511-4.

11. Roelandt T, Heughebaert C, Hachem JP. Proteolytically active allergens cause barrier breakdown. J Invest Dermatol. 2008;128:1878-80.

12. Rahman S, Collins M, Williams CM, Ma HL. The pathology and immunology of atopic dermatitis. Inflamm Allergy Drug Targets. 2011 Aug 25. [Epub ahead of print]

13. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. Curr Probl Dermatol. 2011;41:1-34.

14. Looringh van Beeck FA, Hoekstra H, Brunekreef B, Willemse T. Inverse association between endotoxin exposure and canine atopic dermatitis. Vet J. 2010 Dec 1. [Epub ahead of print]

15. Ezzat MH, Hasan ZE, Shaheen KY. Serum measurement of interleukin-31 (IL-31) in paediatric atopic dermatitis: elevated levels correlate with severity scoring. J Eur Acad Dermatol Venereol. 2011;25:334-9.

16. Niebuhr M, Mamerow D, Heratizadeh A, Satzger I, Werfel T. Staphylococcal α-Toxin Induces a Higher T Cell Proliferation and Interleukin-31 in Atopic Dermatitis. Int Arch Allergy Immunol. 2011;156:412-415.

17. Grimstad O, Sawanobori Y, Vestergaard C, Bilsborough J, Olsen UB, Grønhøj-Larsen C, et al. Anti-interleukin-31-antibodies ameliorate scratching behaviour in NC/Nga mice: a model of atopic dermatitis. Exp Dermatol. 2009;18:35-43.

18. Raap U, Ständer S, Metz M. Pathophysiology of itch and new treatments. Curr Opin Allergy Clin Immunol. 2011;11:420-7.

19. Metz M, Grundmann S, Ständer S. Pruritus: an overview of current concepts. Vet Dermatol. 2011;22:121-31.

20. Tretter S, Mueller RS. The influence of topical unsaturated fatty acids and essential oils on normal and atopic dogs. JAAHA. 2011;47:236-40.

21. Piekutowska A, Pin D, Rème CA, Gatto H, Haftek M. Effects of a topically applied preparation of epidermal lipids on the stratum corneum barrier of atopic dogs. J Comp Pathol. 2008;138:197-203.

22. Fujimura M, Nakatsuji Y, Fujiwara S, Rème C, Gatto H. Spot-on skin lipid complex as an adjunct therapy in dogs with atopic dermatitis: an open pilot study. Vet Med Int. 2011;2011:281846.

23. Popa I, Pin D, Remoué N, et al. Analysis of epidermal lipids in normal and atopic dogs, before and after administration of an oral omega-6/omega-3 fatty acid feed supplement. A pilot study. Vet Res Commun. 2011.

24. Cowden JM, Zhang M, Dunford PJ, Thurmond RL. The histamine H4 receptor mediates inflammation and pruritus in Th2-dependent dermal inflammation. J Invest Dermatol. 2010;130:1023-33.

25. Dijkstra D, Stark H, Chazot PL, et al. Human inflammatory dendritic epidermal cells express a functional histamine H4 receptor. J Invest Dermatol. 2008;128:1696-703.

26. Gutzmer R, Gschwandtner M, Rossbach K, et al. Pathogenetic and therapeutic implications of the histamine H4 receptor in inflammatory skin diseases and pruritus. Front Biosci (Schol Ed). 2011;3:985-994.

27. Mommert S, Gschwandtner M, Gutzmer R, Werfel T. The role of the histamine H4 receptor in atopic dermatitis. Curr Allergy Asthma Rep. 2011;11:21-8.

28. Kim M, Jung M, Hong SP, et al. Topical calcineurin inhibitors compromise stratum corneum integrity, epidermal permeability and antimicrobial barrier function. Exp Dermatol. 2010;19:501-10.

29. Olivry T, DeBoer DJ, Favrot C, et al; International Task Force on Canine Atopic Dermatitis. Treatment of canine atopic dermatitis: 2010 clinical practice guidelines from the International Task Force on Canine Atopic Dermatitis. Vet Dermatol. 2010;21:233-48.

30. Linek M, Favrot C. Impact of canine atopic dermatitis on the health-related quality of life of affected dogs and quality of life of their owners. Vet Dermatol. 2010;21:456-62.

31. Noli C, Colombo S, Cornegliani L, et al. Quality of life of dogs with skin disease and of their owners. Part 2: administration of a questionnaire in various skin diseases and correlation to efficacy of therapy. Vet Dermatol. 2011;22:344-51.

32. Noli C, Minafò G, Galzerano M. Quality of life of dogs with skin diseases and their owners. Part 1: development and validation of a questionnaire. Vet Dermatol. 2011;22:335-43.

Born to Lose: New Tools for Helping Owners Manage Their Obese Pets

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ABSTRACT

Obesity is a growing epidemic in dogs and cats. It is associated with decreased life span, increased risk for various diseases, and derangements in the endocrine control of metabolism and appetite. This article reviews risk factors for obesity, obesity-associated disease, and the altered effects of fat- and gut-derived hormones on obese animals. Treatment of obesity is complicated not only by metabolic abnormalities that predispose obese animals to further weight gain, but also by inaccurate owner perceptions of their pets' body weight and condition. This article reviews the clinical approach to obesity management, including dietary therapy, physical exercise, and pharmacologic intervention.

POINTS TO PUT A FINGER ON

- Recent studies have shown that, after neutering or spaying, dogs and cats undergo significant alterations in multiple hormones that influence appetite, activity, adipose metabolism, glucose tolerance, and lipid metabolism.
- There is increasing evidence that onset of obesity in very young animals is extremely difficult to reverse in later years due to metabolic and hormonal shifts that become more or less "hard-wired."
- Fat is an endocrine organ that secretes a variety of hormones and cytokines collectively termed "adipokines."
- Leptin resistance develops in obese animals, causing decreased metabolism and increased appetite; insulin resistance has the same effect; the orexigenic effect of ghrelin is exaggerated; but sensitivity to PYY is normal. The result is increased appetite and decreased metabolism.
- One of the most important obstacles to weight loss in dogs may be owners' attitudes; dirlotapide (Slentrol®) provides U.S. Veterinarians a tool for obese canine patients and their owners who need additional help in the battle to lose weight.

Obesity—excessive accumulation of adipose tissue in the body—is at epidemic proportions in the United States and worldwide. Despite major public health initiatives spanning several decades, obesity in humans has reached prevalence rates nearing 40% in some states (**Figure 1**). Obesity in dogs and cats has followed this trend. Obesity is loosely defined as body weight 20% above the ideal, or as accumulation of body fat to the extent that it affects the animal's health (1, 2).

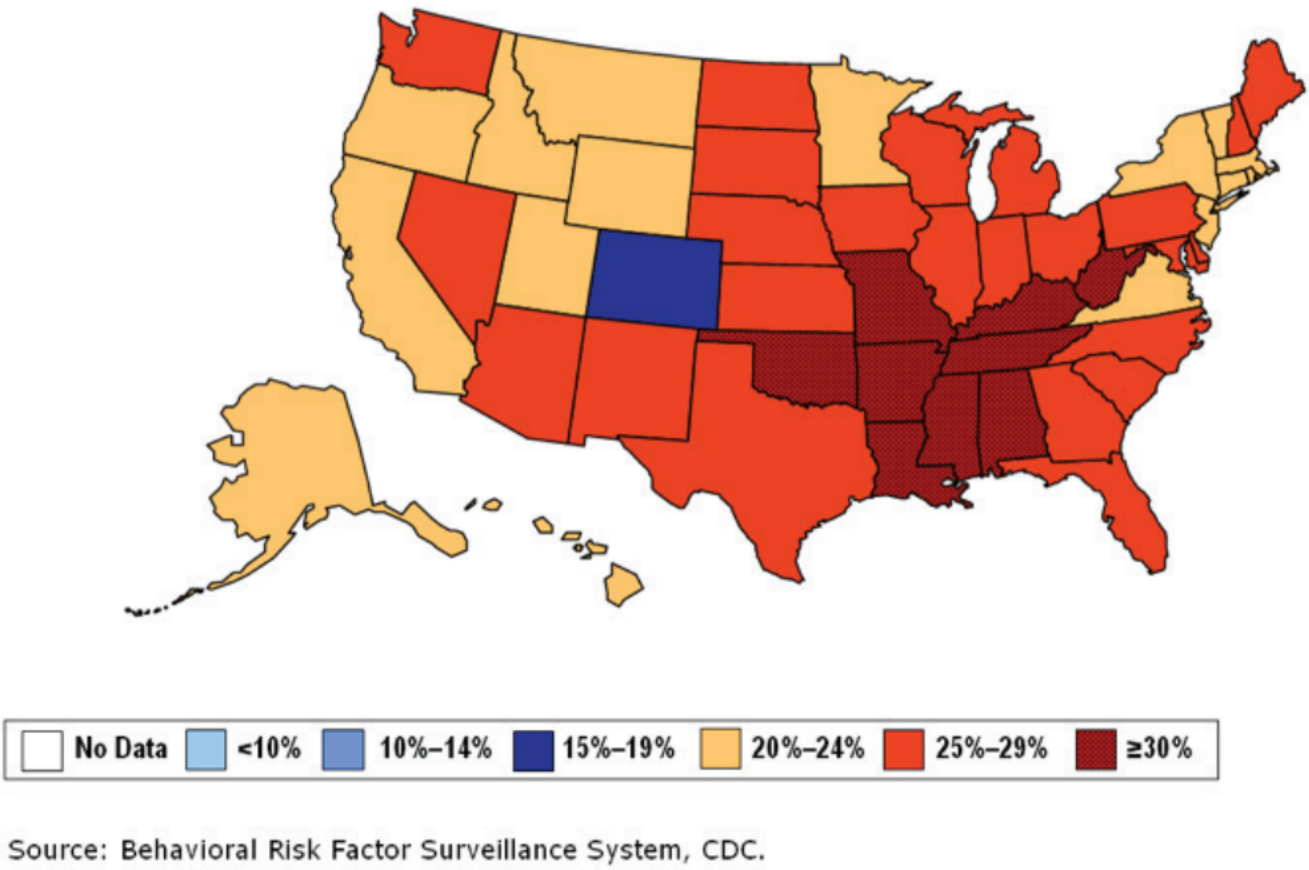

Figure 1: Prevalence of obesity (BMI ≥30) in adults in the United States. (Source: Centers for Disease Control and Prevention)

In humans, more specific criteria have been established for what defines "overweight" and "obese"—these criteria are based on the body mass index. A similar index for optimal body weight has not been identified in dogs, primarily because of the wide variation in body sizes and shapes. More specific methods of assessing accumulation of body fat in dogs are the dual x-ray absorptiometry scan, deuterium oxide analysis, or magnetic resonance imaging, although these methods are expensive, require anesthesia or special equipment, and are not widely available. As a result, they are not helpful in clinical practice (3). However, dogs are generally considered to be overweight when their body weight exceeds their optimal body weight by 20% or if they have a body condition score of 6 or 7, and obese when they are >20% over the optimum or have a body condition score of 8 or 9 (4). In recent years, several programs have been initiated in an attempt to educate the public about obesity and to help veterinarians and pet owners with diet and drug therapy programs. However, the incidence of obesity in the pet population continues to increase despite the many programs that attempt to tackle the problem.

OBESITY-ASSOCIATED DISEASE

Obese human beings generally do not live as long as their lean counterparts and are much more prone to such diseases as type 2 diabetes, coronary artery disease, osteoarthritis, hypertension, and some types of cancer. Obese dogs and cats are susceptible to the same detrimental effects, including decreased lifespan and development of a variety of disorders (**Table**) (5). This was best illustrated in a study of two groups of Labrador retrievers, in which one group had a 25% lifelong reduction in caloric intake compared with the other group (5). In that study, dogs fed less food were leaner and significantly outlived the other dogs. In addition, the incidence of osteoarthritis and hip dysplasia was decreased, and glucose tolerance was improved in the food-restricted group.

Table. Disorders Associated With Obesity

Orthopedic disorders
Osteoarthritis
Fractures (primarily humeral condyles)
Cruciate ligament tears/rupture
Intervertebral disk disease
Joint disorders

Endocrine and metabolic disorders
Hyperadrenocorticism
Hypothyroidism
Diabetes mellitus (cats)
Hypopituitarism
Hyperlipidemia
Insulin resistance
Glucose intolerance
Hepatic lipidosis (cats)

Cardiac and respiratory diseases
Pickwickian syndrome
Tracheal collapse
Laryngeal paralysis
Brachycephalic airway syndrome
Valvular endocardiosis?

Urogenital diseases
Urolithiasis (calcium oxalate)
Urethral sphincter mechanism incompetence
Transitional cell carcinoma
Mammary neoplasia
Dystocia

Other miscellaneous disorders
Heat intolerance
Exercise intolerance
Increased anesthetic risk
Reduced lifespan

There are numerous other obesity-related diseases in dogs and cats—some are caused by obesity and others are exacerbated by it. Such disorders in both species include orthopedic diseases, lipid disorders, urinary incontinence, and a variety of respiratory disorders. Diabetes has been associated with obesity in cats and some types of neoplasia have been strongly associated with obesity in dogs. Veterinarians are familiar with the dramatic decline in the incidence of mammary cancer resulting from ovariohysterectomy in bitches, but that protective effect is often lost as a result of obesity (6). Obesity has also been established as a risk factor for transitional cell carcinoma in dogs (7).

RISK FACTORS FOR OBESITY

There are several risk factors for obesity in dogs. These include breed (e.g., Labrador retriever, cairn terrier, cavalier King Charles Spaniel, Scottish terrier, cocker spaniel), neutering, and several owner behavioral and socioeconomic factors. Owner factors include overhumanizing pets, owner obesity, time spent observing the pet eating, and lower income (5). Interestingly, the type of food a dog is fed is not associated with obesity. A recent study showed that cats gained 40% of their body weight by being fed free-choice food for 3 months after spaying (8). To maintain

prespay body weight, food intake had to be reduced by 30%. Similar studies have demonstrated increased obesity in neutered dogs as well. Following either neutered or spayed dogs, recent studies have shown significant alterations in multiple hormones that influence appetite, activity, adipose metabolism, glucose tolerance, and lipid metabolism (9). In essence, the hormonal changes that occur immediately after neutering result in increased appetite; decreased energy metabolism; and multiple changes in adipocytes and the hormones they secrete that greatly increase the risk for obesity without careful, *early* intervention. One of the key factors for preventing obesity in neutered animals seems to be control of intake immediately after neutering (no free-choice feeding and reduction of intake by 25% to account for the hormonal changes resulting in reduced energy needs), and close monitoring of body weight and body condition score so that individual intake can be adjusted early. Why is this so important? There is increasing evidence that onset of obesity in very young animals is extremely difficult to reverse in later years due to metabolic and hormonal shifts that become more or less "hard-wired." In young animals, control of intake after neutering is critical to prevent metabolic switches.

Some medical conditions (endocrinopathies, such as hypercortisolism and hypothyroidism) and drugs (steroids and anticonvulsants) are associated with obesity. Medical conditions should be considered carefully in the clinical approach to an obese animal. Hypothyroidism is common in dogs and is often suspected as a prime differential in obese dogs. This disease, however, is widely overdiagnosed, and owners are often frustrated when their dogs fail to lose weight despite thyroid hormone supplementation. Hypercortisolism (Cushing's syndrome), on the other hand, may be underdiagnosed. Glucocorticosteroid hormones, endogenous or exogenous, are known to cause increased body fat in many species, and it is important to consider this syndrome as a differential in obese dogs. While genetic factors are also probably involved in the predisposition of some breeds (e.g., Labrador retrievers have a higher incidence of obesity than is seen in other breeds of like size), the role of inheritance in canine obesity needs more study.

"[There is a] popular belief, particularly among lean individuals, that regulation of body weight is largely a matter of willpower. It is hard to imagine such a view of the regulation of any similarly important aspect of physiology, for example blood pressure, persisting for so long."

A.M. Wren and S.R. Bloom
Imperial College London
Gastroenterology. 2007;132:2116-2130.

ENDOCRINOLOGY OF ADIPOSE TISSUE AND OBESITY

Based on the current understanding of fat endocrinology, it is reasonable to consider obesity a true medical disorder rather than simply a lifestyle/willpower issue. Fat is an endocrine organ that secretes a variety of hormones and cytokines (**Figure 2**) (10), which are collectively termed "adipokines." Leptin and adiponectin are the best characterized fat-derived hormones. Leptin is important in regulation of energy balance and satiety. Leptin concentrations in the circulation increase in obesity because of leptin resistance, which results in loss of the beneficial effects of leptin. Adiponectin is a hormone with several functions, but the most important is probably in conferring insulin sensitivity. As body fat increases, adiponectin concentrations drop, contributing to the insulin resistance of obesity. The effects of adiponectin and leptin have been documented in dogs (11–13). Other hormones secreted by fat cells include resistin and vistatin, which are involved in insulin resistance, and apelin, which may contribute to hypertension in obesity. These hormones have not been well-studied in dogs and cats. Vistatin affects insulin secretion.

In addition to hormones, inflammatory cytokines are secreted by adipose tissue. Abnormally increased concentrations of adipose-derived tumor necrosis factor (TNF)-alpha is an example of obesity as a systemic inflammatory condition. Other proinflammatory adipokines are present in obesity as well.

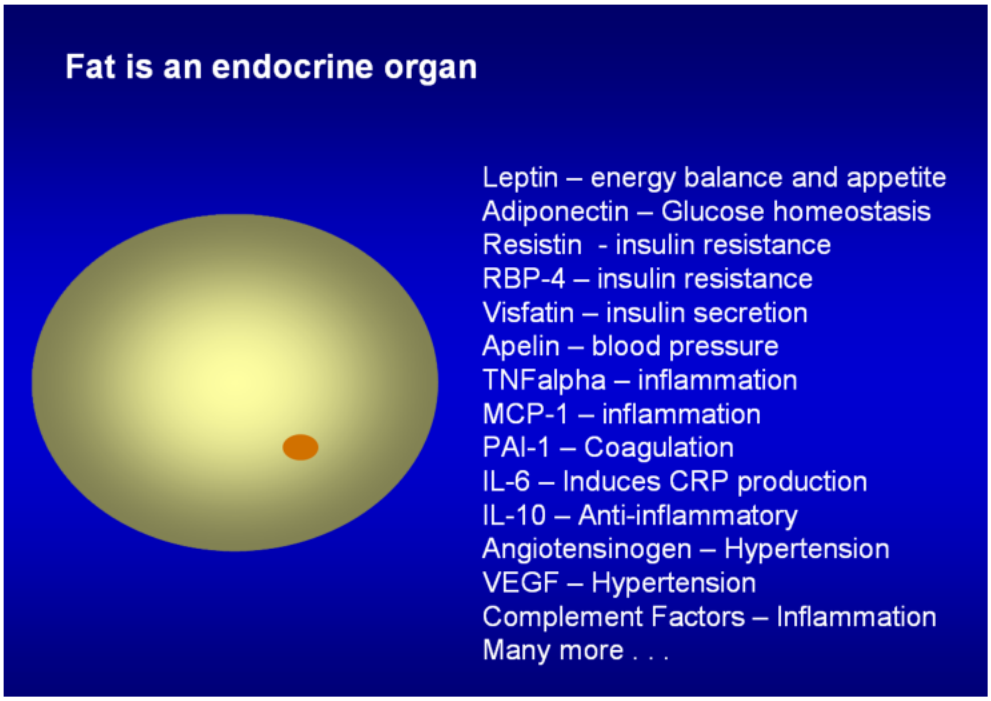

Figure 2
Listed on the right are the many hormones and cytokines secreted by fat cells.

Gut-derived hormones, which are critical for appetite control and glucose homeostasis, are also abnormal during obesity (14). In particular, postprandial elevations of ghrelin, a powerful orexigenic hormone secreted by the gastrointestinal tract, are prolonged in obese human patients (15), although studies of this effect have not been reported in dogs or cats. As a result of ghrelin dysregulation, obese patients need less food but are hungrier, illustrating the vicious cycle of obesity and loss of appetite control. The interplay of appetite and metabolism in normal dogs and the effects of obesity on this process in obese dogs are shown in **Figures 3** through **5**.

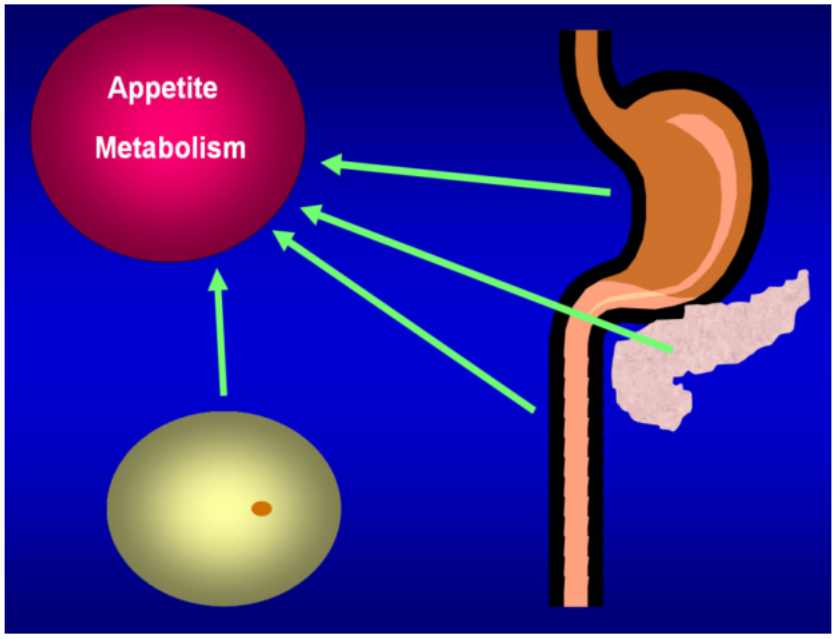

Figure 3
In normal animals, leptin from the adipocyte, insulin from the pancreas, ghrelin from the stomach and peptide YY from the intestine balance appetite and metabolism.

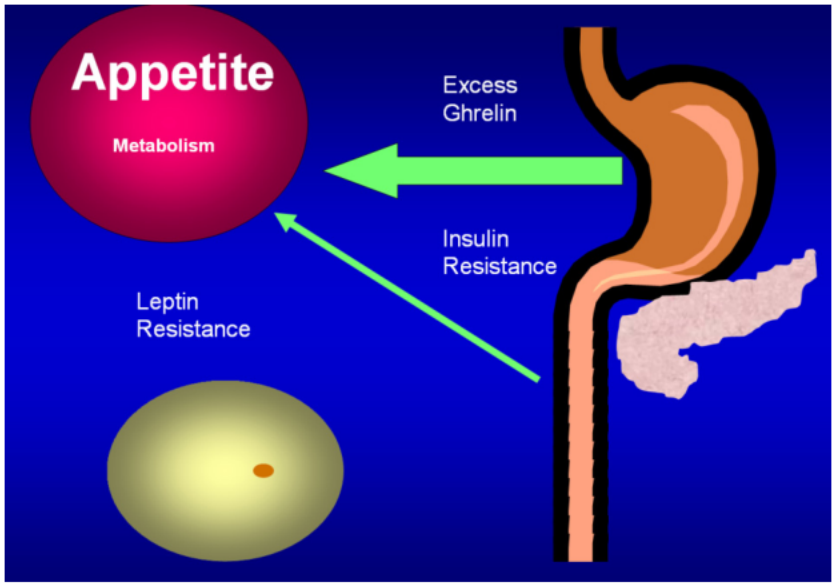

Figure 4
In obese animals, leptin resistance develops, causing decreased metabolism and increased appetite. Insulin resistance has the same effect: The orexigenic effect of ghrelin is exaggerated, but sensitivity to PYY is normal. The result is increased appetite and decreased metabolism.

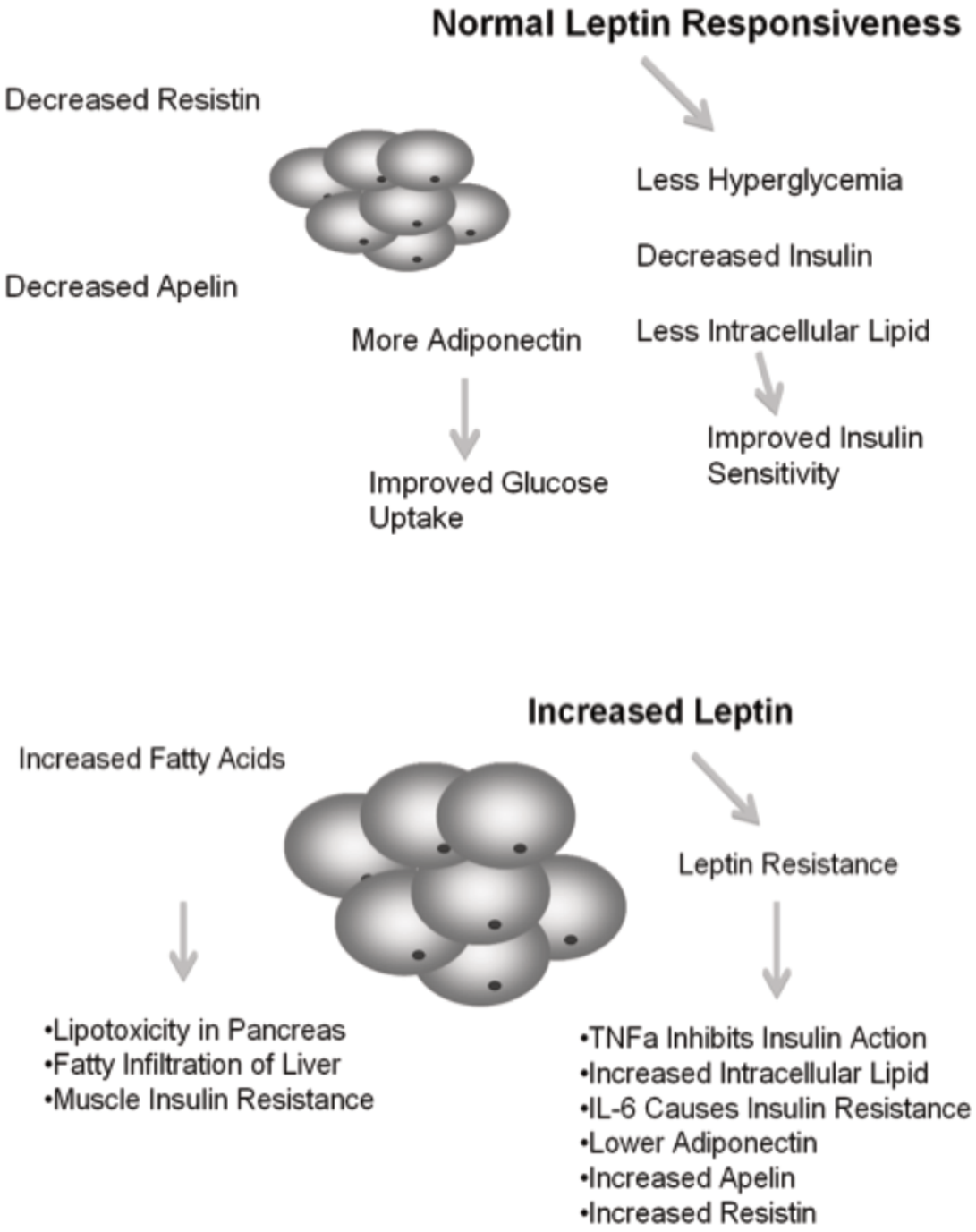

Figure 5
Normal leptin response (*top*) and disturbances in obesity (*bottom*).

In addition to the abnormal endocrine functions of adipose tissue itself, other endocrine systems are affected by obesity. Increased serum thyroid hormone concentrations (16), believed to reflect thyroid hormone resistance, have been documented in canine obesity, as have increases in circulating concentrations of prolactin (17), insulin, and insulin-like growth factor 1 (18). Obese dogs secrete more cortisol in response to adrenocorticotropic hormone stimulation than do lean dogs (17), further illustrating the multisystemic nature of obesity.

TRANSCRIPTOME CHANGES IN OBESE DOGS

We recently published a report of adipose transcriptome changes in a diet-induced obesity model in female dogs (19). In that study, dogs were fed ad libitum for 24 weeks and allowed to become obese. As expected, adipocyte size increased and overfed dogs became severely obese compared with control dogs. The changes in gene expression in adipose tissue during development of obesity were interesting. Microarray analysis showed that there were more than 1600 genes with expression levels affected by obesity. The major functional classes of genes affected by ad libitum feeding and obesity are presented in **Figure 6**. Classes that are most affected include genes involved in transcription, transport, metabolism, intracellular signalling, cell-cycle regulation, RNA processing, and protein degradation. The ramifications of these alterations are not known, but the study demonstrates that development of obesity has significant metabolic, cellular, and genetic consequences.

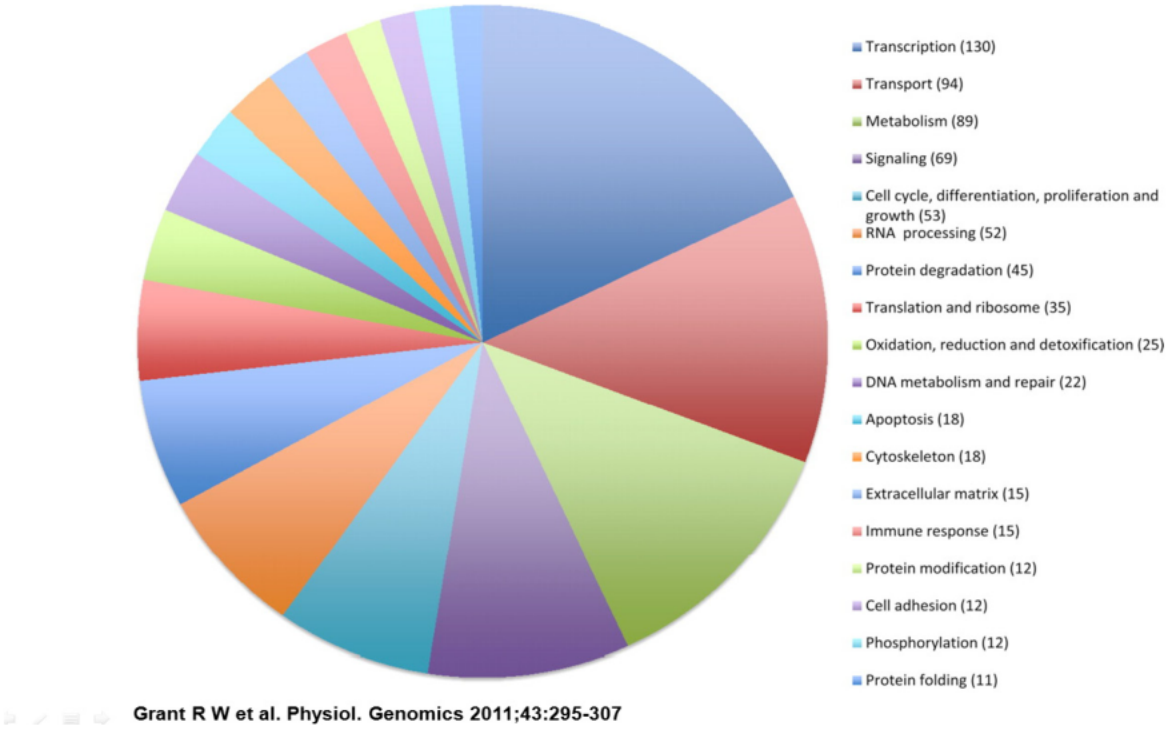

Figure 6
Major functional gene classes affected by ad libitum feeding.

In addition to microarray analysis for differential gene expression in obese dogs, we studied changes in blood metabolites and hormones. As expected, serum concentrations of leptin increased steadily with increasing obesity in the dogs. However, no significant changes occurred in blood concentrations of glucose, insulin, TNF-alpha, C-reactive protein, fructosamine, or adiponectin. These findings were interesting because they suggest that genetic derangements precede detectable changes in some of the traditional hormones and metabolites of interest in the study of obesity. This information may be clinically useful if and when "obesity panels" are developed as clinical tools to monitor and assess risk for obesity in veterinary patients. By the time an obese dog experiences a decline in adiponectin, severe genetic changes have probably already occurred. A deeper understanding of these alterations in gene expression could lead to interventional strategies for treatment of obesity or its associated metabolic abnormalities.

OWNER PERCEPTIONS OF BODY WEIGHT

One of the most important obstacles to weight loss in dogs may be the owner's attitude. We have begun collecting data for a study of owner awareness and attitudes toward obesity in dogs and cats in Chicago. Many studies have shown the phenomenon of erroneous weight perception in parents of obese children (20–23). Although some parents are able to identify their obese children as such, most fail to recognize the condition. This is especially true with parents of younger children (24, 25), and weight misperception can also be affected by certain cultural and socioeconomic factors (26, 27). We hypothesize that owners probably also fail to perceive obesity in their pets, and there is a lack of concern for its health consequences. To test this hypothesis, we are currently comparing owner perception of a pet's body condition with body condition assessed by a veterinarian skilled in body condition scoring. We seek to determine whether pet owners perceive any adverse health risks associated with obesity in their pets. We are also investigating the effects of owner gender, age, and breed of the pet on accuracy of weight perception. While the study is not complete and the data have not been fully analyzed, we have enrolled a large number of study subjects, and preliminary data indicate that pet owners are no better at recognizing obesity or excess body weight in their pets than are parents of obese children. Roughly half of the pets in our study are overweight or obese, but very few owners see their pet's body condition as anything other than ideal. Men and women appear to be equally poor judges of their pets' body condition. Our preliminary results seem to indicate that even when pet owners recognize obesity, they are usually not concerned about the effects of obesity on their pets' health. This means that veterinarians have a serious challenge in approaching the topic of pet obesity with their clients. It is important to find ways to help owners recognize the scope and the consequences of obesity.

AN OBESITY PANEL AS A POSSIBLE CLINICAL TOOL

Clinical tests to quantify the deleterious effects of excess body fat could be one tool that helps pet owners recognize the impact of obesity on their pets' health. Biomarkers for obesity-related health problems are a current topic of interest among veterinary nutrition researchers (28). Measurement of adipokines, lipids, inflammatory mediators, and other molecules associated with obesity could be used to identify comorbidities in obese dogs. Biomarkers could also be used to identify patients at risk for obesity-related problems or for the development of obesity, and they could have value in monitoring the response to obesity therapy. Panels of obesity biomarkers are available for use in human and rodent obesity research but have not been applied extensively to clinical work in obese patients. Possibly useful components of an obesity panel would include adiponectin, insulin, TNF-alpha, monocyte chemoattractant protein-1, resistin, apelin glucose, fructosamine triglycerides, leptin, ghrelin, and PYY. Further research is needed in this area.

DIETARY THERAPY

In order for dietary therapy to be successful, several caveats must be considered: 1) Dietary therapy must be individualized (e.g., dietary needs for allergy, renal disease, gastrointestinal issues), 2) calories must be restricted without concurrent protein restriction to prevent loss of lean muscle tissue, and 3) consideration must be made for the fact that it will take time to reduce energy intake below the individual's metabolic rate so that loss of fat mass is not accompanied by loss of lean body tissue (29). The first step in making a diet plan is to obtain a complete dietary history (as much as possible, but in cats fed free-choice this can be impossible) that gives an accurate accounting of all foods fed to a pet on a typical day. In some cases, it may be necessary to have the owners keep a diet log for a week, writing down the meals, the treats, the table foods—anything consumed by the dog during that time. This is especially helpful in households where the dog may receive foods from more than one individual (especially children). If the dog has access to any other foods (other pets in the family, outside scavenging), if the pet received medications in foods, and if there are other food items available to the dog (e.g., chew treats, dental chews) should also be noted.

The next step in designing a diet plan is to decide upon a weight loss goal. The goal does not necessarily have to be achievement of ideal body weight—the goal should be based on the pet, the owner's situation and goals, and the ability to reach the goal. In orthopedic studies in humans and dogs, small reductions in body weight significantly reduced lameness, pain, and inflammatory cytokine levels (30). It is important to set reasonable, achievable goals rather than overly ambitious ones that are just going to result in the client becoming discouraged when the pet does not reach

the goal. A step-down approach to weight loss is much more likely to result in success and continued owner persistence than an overly ambitious goal that results in the owner abandoning the process due to lack of progress. Once you have set the appropriate weight loss target for that pet, you can calculate the energy restriction that will be required to achieve the goal. Ideally remember, in obese pets, energy metabolism is significantly reduced, and while not yet studied extensively in dogs, in most obese cats, a reduction of intake by 20%–40% below resting is often required achieve any weight loss. Obviously this degree of restriction cannot be made quickly, and must be done with the goal of preventing protein malnutrition and nutritional deficiencies that may occur from feeding a very small amount of a restrictive diet. Ideally, to start the process, the new energy intake should be 10%–20% less than the pet's current intake. If current intake is not known (or cannot be calculated accurately), then it is necessary to estimate intake for the target weight. There are several equations that can be used to calculate energy requirements; however, there is wide variation among animals for energy requirements, and the metabolism in obese dogs is less than that of normal dogs. In other words, most obese dogs will need to eat significantly less than resting energy [(BW/kg x 30) + 70] to lose weight. So, calculation of needs is only a starting point from which to make adjustments. Target weight loss should be a 5%–10% reduction in weight per month, with intake adjusted downward on the basis of the dog's response to your changes. Nevertheless, no matter which approach is used, the key to success is to have complete client cooperation, to monitor the pet frequently (e.g., every 3–4 weeks), and finally to make adjustments in intake as needed based on your plan.

In addition to setting a goal and calorie target, it is important to select the weight loss diet carefully. Many therapeutic diets have been formulated for weight loss, and most are based on the idea that low-fat, high-fiber diets are the best diets for dogs undergoing weight loss. There is no question that these diets are quite effective and have been used for many years in weight loss programs; however, they involve certain considerations for the overall diet planning. First, preservation of lean body mass is important to prevent starvation metabolism and weight rebound in dogs with extremely restricted intake. Thus, the diet chosen must have both significant quantities of protein (i.e., not a moderate- or low-protein diet) and the protein is high-quality (i.e., of high biological value and highly digestible). This point is particularly important in dogs consuming high-fiber diets, as insoluble fiber reduces the digestibility of nutrients and may increase the risk for protein deficiency. No specific dietary protein requirement has been established for dogs undergoing significant weight loss, but weight loss diets without at least 20%–25% protein may be limiting in patients requiring severe energy restriction to achieve weight loss.

EXERCISE: INCREASE MUSCLE AND METABOLISM

In addition to reducing the energy intake of overweight pets, it is possible to expedite weight loss by increasing energy expenditure through increased exercise. Further, and probably most important, muscle mass is a critical factor in determining metabolic rate and energy utilization. In obese humans, exercise alone is rarely sufficient to effect weight loss, but without increasing muscle mass by increasing activity, it is very uncommon for energy demands to be requited. Similarly, in obese dogs it is important to start slowly with an exercise program and very gradually and slowly increase duration and intensity. In some dogs, exercise may be impossible due to severe joint problems, exercise intolerance, or owner inability to exercise with the pet. In these dogs, very minimal activity, or low-impact activity, such as swimming or water treadmill, may be needed to allow safe, nonpainful exercise. Consultation with a veterinary physical rehabilitation specialist is often very helpful in determining appropriate activities for the dog. This can also be part of the overall diet and weight reduction plan, as the weigh-ins and evaluation of the pet's progress can occur in conjunction with the rehabilitation visits.

Many dogs become obese due to the social bonding that occurs with owners and their dogs during feeding. This human–animal bonding results in a strong behavioral component to the development of obesity that must be addressed (31). To be successful in changing these behaviors, it is important to substitute low-calorie treats, games, or other interactive activities for table scraps or other high-calorie treats; also, begging for food has more to do with behavior than hunger. If this relationship is not considered in weight loss programs, the plan is doomed to meet significant obstacles. In some cases, consultation with a veterinary behaviorist is an important part of the overall plan for weight loss.

APPETITE SUPPRESSION: DRUG THERAPY CAN HELP

Management of obese dogs has long been focused on reducing energy consumption (dietary management) and increasing energy expenditure (exercise). Although this approach is very effective when it is implemented early and comprehensively, it can be quite difficult to overcome the behavioral, social, metabolic, and hormonal influences of obesity to achieve long-term success. Another challenge to weight loss is the irreversible increase in the number of adipocytes associated with obesity. During obesity, adipocytes increase in size as well as number; however, during weight loss, size decreases but the number does not (**Figure 7**).

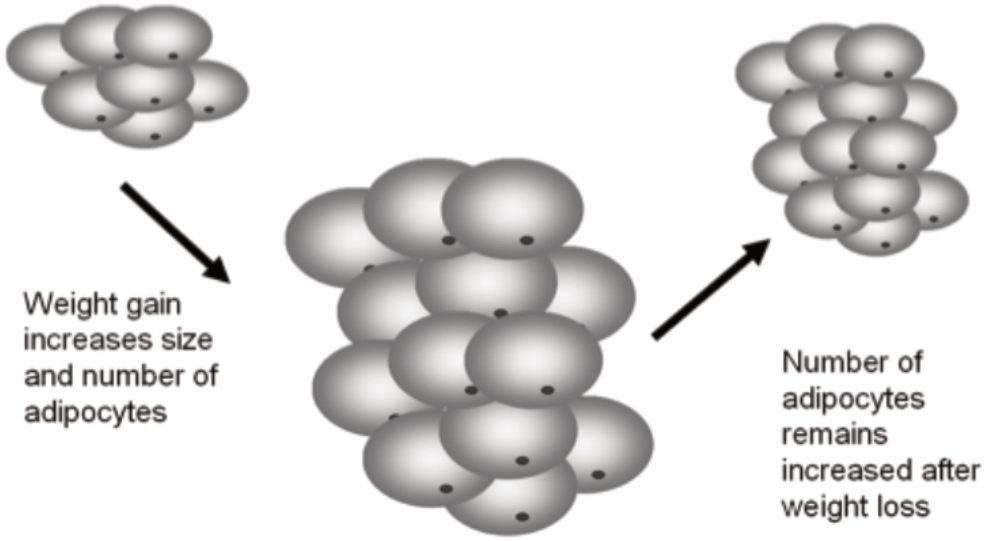

Figure 7
Weight gain and weight loss.

In humans, obesity management options include dietary management, exercise, behavior modification, pharmacologic therapy, and surgery. The surgical approach is aimed at both reducing stomach capacity and reducing appetite (by reducing hormones secreted by eating and from the stomach). With the availability of dirlotapide (Slentrol®), veterinarians in the united states have a tool for obese canine patients and their owners.

CLINICAL EXPERIENCE WITH SLENTROL: HOW DOES IT WORK?

Dirlotapide is a selective (intestinal) microsomal triglyceride transfer protein (MTP) inhibitor. This means that the drug reduces absorption of fat from the small intestine by slowing the packaging of fatty acids with protein to form chylomicrons, a process that occurs inside enterocytes using the enzyme MTP (**Figure 4**) (32), and fat absorption is reduced. Although this reduction is responsible for only a small percentage of the weight lost by dogs on the drug, it is this effect that triggers an increase in release of PYY—a potent appetite suppressant and satiety hormone. Ultimately, the primary effect of dirlotapide in achieving weight reduction is that it reduces appetite and thus helps dogs lose weight by reducing the begging, ravenous appetites, and food-seeking behaviors that are common during the calorie reduction needed to lose weight. This is the key benefit of adding dirlotapide to diet and exercise. It helps overcome one of the biggest obstacles to effective weight loss: controlling intake—which can be quite difficult when obesity hormones and energy metabolism in the dog are abnormal.

REFERENCES

1. Diez M, Nguyen P. The epidemiology of canine and feline obesity. Waltham Focus. 2006;16: 2-8.

2. Lund EM, Armstrong PJ, Kirk CA, et al. Prevalence and risk factors for obesity in adult dogs from private veterinary practices in the United States. Int J App Res Vet Med. 2006;4:177-187.

3. Mawby DI, Bartges JW, d Avignon A, et al. Comparison of various methods for estimating body fat in dogs. JAAHA. 2004;40:109-114.

4. Burkholder WJ. Precision and practicality of methods assessing body composition of dogs and cats. Comp Cont Educ Pract Vet. 2001;23:1-10.

5. Kealy RD, Lawler DF, Ballam JM, et al. Effects of dietary restriction on life span and age-related changes in dogs. JAVMA. 2002;220:1315-1320.

6. Sonnenschein EG, Glickman LT, Goldschmidt MH, McKee LJ. Body conformation, diet, and risk of breast cancer in pet dogs: a case-control study. Am J Epidemiol. 1991;133:694-703.

7. Glickman LT, Schofer FS, McKee LJ, Reif JS, Goldschmidt MH. Epidemiologic study of insecticide exposures, obesity, and risk of bladder cancer in household dogs. J Toxicol Environ Health. 1989;28:407-414.

8. Kienzle E, Bergler R, Mandernach A. A comparison of the feeding behavior and the human-animal relationship in owners of normal and obese dogs. J Nutr. 1998;128(12 Suppl):2779s-2782s.

9. Zoran D: Personal observation; 2011.

10. Belsito KR, Vester BM, Keel T, Graves TK, Swanson KS. Impact of ovariohysterectomy and food intake on body composition, physical activity, and adipose gene expression in cats. J Anim Sci. 2009;87:594-602

11. Vázquez-Vela ME, Torres N, Tovar AR. White adipose tissue as endocrine organ and its role in obesity. Arch Med Res. 2008;39:715-728.

12. Gayet C, Leray V, Saito M, et al. The effects of obesity-associated insulin resistance on mrna expression of peroxisome proliferator-activated receptor-gamma target genes, in dogs. Br J Nutr. 2007;98:497-503.

13. Ishioka K, Omachi A, Sagawa M, et al. Canine adiponectin: cdna structure, mrna expression in adipose tissues and reduced plasma levels in obesity. Res vet Sci. 2006;80:127-132.

14. Wren AM, Bloom Sr. Gut hormones and appetite control. Gastroenterology. 2007;132:2116-2130. Review.

15. Erdmann J, Leibl M, Wagenpfeil S, Lippl F, Schusdziarra V. Ghrelin response to protein and carbohydrate meals in relation to food intake and glycerol levels in obese subjects. Regul Pept. 2006;135:23-29. Epub 2006 apr 27.

16. Yamka Rm, Friesen KG, Frantz NZ. Identification of canine markers related to obesity and the effects of weight loss on the markers of interest. Intern J Appl Res Vet Med. 2006;4:282-292.

17. Martin LJM, Siliart B, Dumon HJW, et al. Hormonal disturbance associated with obesity in dogs. J Anim Physiol Anim Nutr. 2006;90:355-360.

18. Gayet C, Bailhache E, Dumon H, et al. Insulin resistance and changes in plasma concentration of TNF, IGF-1, and NEFA in dogs during weight gain and obesity. J Anim Physiol Anim Nutr. 2004;88:157-165.

19. Grant RW, adipose tissue transcriptome changes during obesity development in female dogs. Physiol Genomics. 2011;43:295-307.

20. Vuorela N, Saha MT, Salo MK. Parents underestimate their child` s overweight. Acta Paediatr. 2010;99:1374-1379.

21. Etelson D, Brand DA, Patrick PA, Shirali A. Childhood obesity: do parents recognize this health risk? Obesity Res. 2003;11:1362–1368.

22. Eckstein KC, Mikhail LM, Ariza AJ, Thomson JS, Millard SC, Binns HJ. Parents' perceptions of their child's weight and health. Pediatrics. 2006;117:681-690.

23. Doolen J, Alpert PT, Miller SK. Parental disconnect between perceived and actual weight status of children: a metasynthesis of the current research. J Am Acad Nurse Pract. 2009;21:160-166.

24. Júlíusson PB, Roelants M, Markestad T, Bjerknes R. Parental perception of overweight and underweight in children and adolescents. Acta Paediatr. 2011;100:260-265.

25. Rudolph H, Blüher S, Falkenberg C, et al. Perception of body weight status: a case control study of obese and lean children and adolescents and their parents. Obes Facts. 2010;3:83-91.

26. Jimenez-Cruz A, Bacardi-Gascon M, Castillo-Ruiz O, Mandujano-Trujillo Z, Pichardo-Osuna A. Low income, mexican mothers' perception of their infants' weight status and beliefs about their foods and physical activity. Child Psychiatry Hum Dev. 2010;41:490-500.

27. Guendelman S, Fernald LC, Neufeld LM, Fuentes-Afflick E. Maternal perceptions of early childhood ideal body weight differ among mexican-origin mothers residing in mexico compared to california. J Am Diet Assoc. 2010;110:222-229.

28. Armstrong PJ. Are adipokines functional biomarkers of obesity? Proceedings of the Companion Animal Nutrition Summit: Focus on Obesity and Obesity-Related Diseases. Tucson, AZ; 2011:26-32.

29. Zoran DL. Feline obesity: clinical recognition and management. Comp Cont Educ Pract Vet. 2009;31:59-70.

30. Mlacnik e, bockstahler ba, müller m, tetrick ma, nap rc, zentek j. Effect of caloric restriction and a moderate or intense physiotherapy program for treatment of lameness in overweight dogs with osteoarthritis. JAVMA. 2006;229:1956-1960.

31. Yaissle JE, Holloway C, Buffington CA. Evaluation of owner education as a component of obesity treatment programs for dogs. JAVMA. 2004;224:1932-1935.

32. Wren JA, King VL, Campbell SL, Hickman MA. Biologic activity of dirlotapide, a novel microsomal triglyceride transfer protein inhibitor, for weight loss in obese dogs. J Vet Pharmacol Ther. 2007;30(Supp):33-42.

Maximizing Benefit and Minimizing Risks in Canine Osteoarthritis Management

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ABSTRACT

Osteoarthritis (OA) is one of the most common diseases of dogs. It causes pain, decreased mobility, and decreased quality of life. It is progressive, and yet the effects of this disease are often ignored until they become obvious, at which time reactive, short-term treatment is provided. The lack of efficacy of this approach leads to frustration on the part of both owner and veterinarian. The OA-associated pain is central to the multidimensional adverse effects of this disease. Effecting predictable pain relief should be the primary focus of symptomatic treatment at every stage. At all stages, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most predictable analgesics. Regardless of the stage of disease or the treatments selected, the practitioner should aim to maximize the benefit and minimize the risks of managing OA. This paper discusses the adverse multidimensional effects of OA and gives an overview of the approach to treatment. It focuses on ways to use NSAIDs to maximize their benefits and minimize their risks.

POINTS TO PUT A FINGER ON

- Pain is the central feature driving the multidimensional adverse effects of osteoarthritis (OA).
- Effective pain treatment can only be achieved over the long term due to the presence of central sensitization in chronic OA.
- A comprehensive assessment of the OA patient will allow different treatment strategies to be prioritized.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most predictable and efficacious means of providing pain relief in OA.
- The benefit of NSAIDs can be maximized by using them early in the disease process and as part of a multimodal approach and long-term as opposed to short-term therapy.
- The risks of NSAIDs can be minimized through careful attention to concurrent drug administration, screening patients for risk factors, dosing appropriately, and communicating fully with clients.

Management of osteoarthritis (OA) has become increasing complex in the past decade. There are many recommendations for treating the associated pain and dysfunction, including but not limited to surgical intervention, systemic medical therapy (base analgesics, adjunctive analgesics), local medical therapy (transcutaneous, intra-articular), home- and clinic-based exercises, weight optimization, nutritional supplementation, massage, acupuncture, laser therapy, heat/cold therapy, neuromuscular electrical stimulation, transcutaneous electrical stimulation, and joint mobilization. However, it should be remembered that OA in dogs is a multifaceted problem—indeed, it is becoming recognized that OA presents differently in growing, middle-aged, and older dogs. OA presenting at different life-stages requires different approaches to optimize care. For example, in growing dogs surgical intervention may be the best option to try to limit disease progression and the likelihood of pain in the near and distant future.

Regardless of the stage of disease or the treatments selected, the practitioner should aim to maximize the benefits and minimize the risks of managing OA. The mainstay of treatment involves methods to alleviate pain, and at all stages of OA, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most predictable analgesics.

CAUSES

The cause of OA in a particular joint may be obscure and extends beyond any obvious cause. For example, hip dysplasia is considered a cause of coxofemoral joint OA, but whether hip dysplasia leads to OA pain depends on many factors, not all of which are completely understood. Currently proposed models to explain the occurrence of OA indicate that each individual has an inherent susceptibility to OA, and superimposed on this are local factors at the joint level. A schematic summary of this model is shown in **Figure 1**.

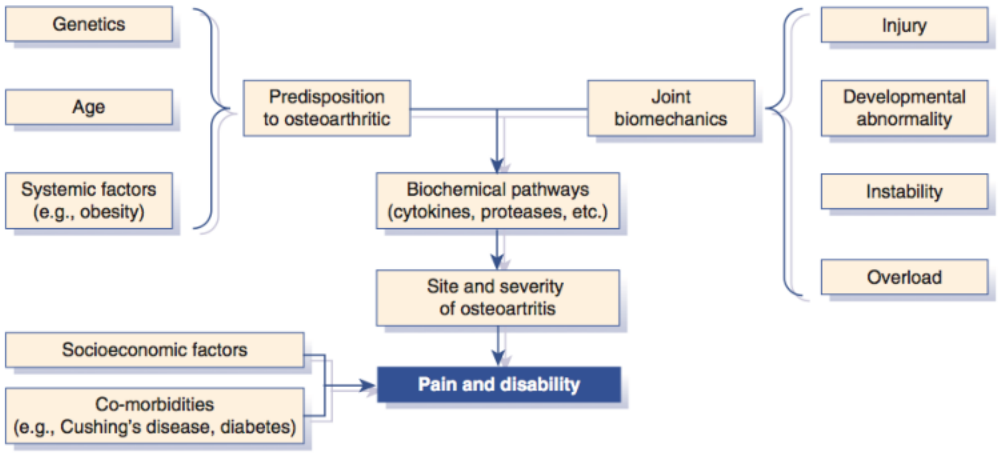


Figure 1
In this model, individual susceptibility to OA is determined by genetics, age, and such systemic factors as obesity. The genes that control this susceptibility have not been identified in dogs; however, some progress has been made in understanding of the genetic basis of diseases that cause secondary OA (such as cruciate disease and hip dysplasia). However, some simple environmental factors that we can control, such as overfeeding, have been shown to clearly affect development of OA (1, 2). *(Adapted from Lohmander LS, Dieppe PA. Pathogenesis and management of pain in osteoarthritis. Lancet. 2005;365:965.)*

CONSEQUENCES

The negative effects of OA involve the following four broad categories:

- Pain (adverse sensory and emotional experience)
- Mobility (the ability to move freely)
- Activity (the ability to perform specific activities)
- Affective effects (mood, feelings).

Within each of these areas, we recognize physiologic changes, which manifest most obviously as varying degrees of compromise of the musculoskeletal system. Not all of these categories are equally important in all patients—indeed, they are not all present in all patients. From an assessment point of view, the degree of compromise of the function and state of the musculoskeletal system tell us most about the severity of individual OA pain.

PREVENTION AND TREATMENT

Overall, OA management falls into two broad categories—prevention and treatment. The first goal is to prevent or minimize development of the disease and its associated pain. Much research has been devoted to finding a way to reverse the disease process, but so far none have been successful. Treatment is aimed at minimizing the clinical signs of OA: pain and related changes in the musculoskeletal system. Effective pain management is central to successful

treatment.

Prevention strategies include screening (e.g., PennHip scheme) and breeding approaches to try to minimize risk-associated genes in the population, surgery to correct limb and joint deformities, and lifestyle modifications (exercise and nutrition). Treatment strategies are aimed at decreasing the clinical signs associated with OA pain and dysfunction. Treatments are summarized in **Box 1**.

Box 1. Treatments for OA-Associated Pain

Nonsurgical, nonmedical
- Weight management
- Diet modulation (type; amount)
- Exercise
- Physical rehabilitation and physical modalities
- Environmental modification
- Gold implantation
- Nutritional supplements
- Acupuncture

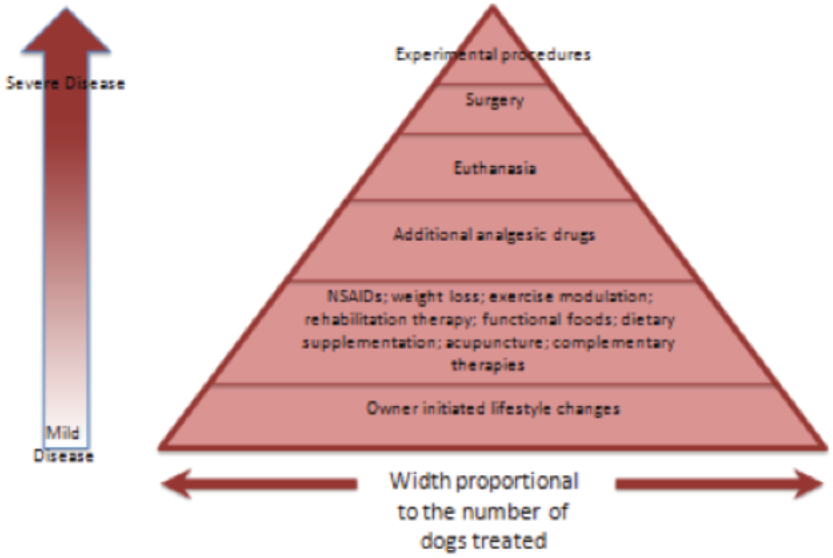
Surgical
- Joint replacement (hip, elbow, knee)
- Excision arthroplasty
- Arthrodesis
- Joint denervation
- Stem cell therapies

Medical
- "Base" analgesics (NSAIDs, acetaminophen, steroids)
- Adjunctive analgesics (e.g., tramadol, amantadine, gabapentin, tricyclic antidepressants)
- Postulated disease modifying drugs
- Chemical desensitization
- Neuroablative procedures

OA management is usually conservative and multimodal. **Figure 2** summarizes the relationship between use of common treatments and disease severity. The vast majority of cases are managed with NSAIDs, combined with nutrition, weight management, and exercise. Indeed, these treatments should be considered the cornerstones of managing OA pain and are best used in conjunction.

Figure 2

Current management of canine OA. Large numbers of patients are managed with conservative measures, the mainstays of which are NSAIDs, exercise, and dietary modulation. Patients with more severe OA pain and disability may require additional analgesia or, if the condition is very severe, euthanasia or surgery



depending on clinical and economic factors, as well as the client's desires. The pyramid is not supposed to represent a step-wise approach to the treatment of OA pain—rather, it shows the relative numbers of dogs treated with particular broad approaches. It demonstrates that treatment with NSAIDs, exercise, and nutritional modulation are commonly used and important. *(Adapted from Innes JF. Arthritis. In: Tobias K, Johnston S, eds. Small Animal Surgical Practice. In press.)*

Before initiating any therapy, the practitioner should comprehensively assess the OA patient. Evaluating the initial severity of pain and disability and monitoring the response to treatment are crucial for effective management of pain and disability. With so little evidence on the efficacy of most suggested therapies, this becomes even more important in the individual animal. **Box 2** outlines a comprehensive approach to assessment.

Box 2. Evaluating the Canine OA Patient

Evaluation of the canine OA patient consists of a veterinary assessment or examination, combined with the owner's assessment.

The overall assessment of the negative impact of OA involves evaluation of 4 broad categories:

- Pain (adverse sensory and emotional experience)
- Mobility (the ability to move freely)
- Activity (the ability to perform specific activities)
- Affective effects (mood, feelings).

All categories are interconnected and together result in deterioration of the musculoskeletal system.

Careful assessment of these 4 categories and their adverse effects will guide us in being able to prioritize treatment strategies. To fully assess these 4 categories, the clinician needs to gather data on:

- Body balance, muscle mass, muscle health
- Ease of movement and mobility
- Gait and limb use
- Joint-associated pain and mobility
- Other factors affecting mobility
- Ability to perform specific activities
- Level of engagement, mood

Obviously, such a complete assessment involves input from both the veterinarian and the owner.

Making this type of assessment is necessary to be able to move ahead with treatment choices and for evaluating treatment efficacy. One also needs to be aware of whether other disease is present that may impact the efficacy of treatment for OA-associated pain.

In practical terms, the required data can be gained by moving through a few logical steps:

Body Balance and Degree of Muscle Mass
Overall muscle mass of the fore- and hindlimbs and of each limb individually should be assessed. General body balance should be assessed at the same time—for example, a dog that stands with its forelimbs angled back under its torso and has a relatively small "back end" is having problems with its hindlimbs or caudal spine. Many of these observations can be made by simply watching the dog in the consulting room. Compare to the opposite limb if appropriate. Severe muscle wasting should alert the clinician to the possibility of a neurologic component. Muscle mass can be evaluated using both hands, evaluating specific muscle bellies of both limbs simultaneously. Alternatively, or in addition, limb girth can be measured using a specially designed tape measure and recording the result. Such measurements must be taken the same way every time for consistency. Simply, together with the response to palpation, this parameter can give valuable information on limb-associated discomfort. Muscle wasting occurs with decreased limb use (both due to pain and mechanical factors).

Ease of Movement, Mobility, Gait, and Limb Use
Ease of movement and mobility is assessed as the dog enters the consulting room and moves around. These observations are often more informative about the overall disability of the dog than for specific limb lameness. Recording the degree of lameness is still considered an important part of the evaluation and follow-up, especially when a single limb is predominantly affected. One often-overlooked way to assess limb comfort and lameness is to evaluate standing bodyweight distribution. In the author's experience, this can often be a more sensitive measure of limb comfort and can be assessed easily in the examination room as part of the patient history.

Severity of Pain Associated with Affected Joints
Flexion, extension, rotation, and mediolateral stressing joints and evaluating the response can give some indication to the discomfort associated with that joint during mobility. The following scale can be used to record the level of reaction:

Pain Scale Based on Palpation

0: No resentment; normal amount of body or limb movement, wriggling, and restlessness.

1: Mild withdrawal; mild resistance; shows mild indications of discomfort, such as ceases panting, raises head, withdraws limb or moves away.

2: Moderate withdrawal; body tenses; may orient to site; may vocalize or increase vocalization.

3: Orients to site; forcibly withdraws from manipulation; may vocalize or attempt to bite.

4: Tries to escape/prevents manipulation; bites; markedly guards area.

This scale is not very sensitive, but it enables categorization of the discomfort into broad, clinically relevant categories. It also helps determine which joints are most likely problematic.

Evaluation for Other Disorders
At this stage, it is important to evaluate the patient for other diseases and consider the possibility of the presence of other factors that can contribute to lameness or mobility or activity impairment, such as:

Neurologic disease: The patient should have a neurologic evaluation—for example, many older retriever-type dogs have concurrent hindlimb OA and degenerative neuropathy. Eliminating the pain associated with the OA may not significantly improve function in these dogs.

Spinal pain: Associated with spinal degenerative joint disease, such as intervertebral disk disease (not necessarily associated with neurologic deficits), lumbosacral degenerative joint disease, sacroiliac degenerative joint disease.

Muscle spasm: OA-associated pain leads to altered limb use, altered methods for limb stabilization and control, and

altered body carriage. These compensations can lead to muscle spasm and associated pain. For example, some dogs with hip dysplasia and secondary OA can exhibit significant iliopsoas pain. Most dogs with bilateral hindlimb OA pain will have some degree of paralumbar muscle spasm and pain. Dogs with bilateral forelimb OA pain often exhibit neck and parathoracic spinal muscle spasm and pain. As yet, there are no accepted or validated methods to assess muscle spasm or pain, so simple palpation at varying degrees of pressure is used for evaluation.

Systemic disease: Such diseases as hypothyroidism and hyperadrenocorticism can affect mobility through a variety of mechanisms.

Dermatologic disease: Skin disease can affect mobility, especially if it significantly affects the feet.

Obesity: Bodyweight and body condition score should be an integral part of OA assessment. Obese patients have more bodyweight, and this can limit mobility. In addition, it is becoming increasingly recognized that fat can induce a pro-inflammatory state by virtue of the pro-inflammatory cytokines and mediators spontaneously produced by fat cells. Such mediators are believed to potentiate pain from diseased tissues, and facilitate "pain-processing" by the central nervous system.

Owner Evaluation of Mobility and Pain
Evaluation of pain and disability associated with canine OA is challenging because interpretation of physical examination findings (e.g., pain response) is difficult, radiographic signs do not predict disease or disability, the disease changes slowly, disability progresses slowly, and individual interventions may have relatively small effects. Owner assessment is used at the start of treatment to define the degree of disability and to help decide the level of treatment required; the owner should also be utilized to monitor treatment efficacy. It is likely that the next few years will see online versions of these instruments being validated for remote monitoring of patients.

Validated Questionnaires
Owner-completed questionnaires (clinical metrology instruments) have been used as outcome measures in human OA for a substantial length of time. Examples include the WOMAC and the Lequesne Index. These instruments have been extensively validated, often in many languages.

At the present time, the most validated instruments available are:

1. Canine Brief Pain Inventory: http://research.vet.upenn.edu/PennChart/AvailableTools/CBPI/tabid/1970/Default.aspx
2. Helsinki Chronic Pain Index—available on request to author: Anna Hielm-Bjorkman: Anna.Hielm-Bjorkman@helsinki.fi)
3. Texas VAS Instrument—available on request to author: Sharon C. Kerwin skerwin@cvm.tamu.edu)
4. Liverpool Osteoarthritis in Dogs: www.liv.ac.uk/sath/services/LOAD.pdf

Between the clinician and owner assessment, the multidimensionality of the effects of OA can begin to be appreciated, and treatment can be tailored and prioritized.

EVIDENCE OF EFFICACY OF TREATMENTS

There is no known cure for OA, and management is often multimodal, incorporating pharmacotherapy (e.g., NSAIDs, other analgesics), nutraceuticals, functional foods, physical therapy, and alternative therapies (e.g., acupuncture) (**Box 1**). Surgery has also been used to manage canine OA for both slowing disease progression or for whole joint replacement. The many and varied therapies suggested for management of pain, and the ease with which claims of efficacy can be made, make it difficult for the practitioner to know what treatments are associated with real, predictable efficacy. Studies reporting the efficacy of such treatments are spread across many journals, and published information can be of such poor quality that the results are misleading. For example, most treatments for OA pain, when prescribed by a veterinarian, will have positive effects in the minds of most owners—the placebo effect. Unless studies are properly designed and executed, there can be little confidence in the results. In the same manner, the claims of opinion leaders are just that: opinions. At best, false claims of efficacy are made; at worst, dogs in need of predictable relief receive

ineffective treatments.

Systematic reviews are useful to remind practitioners where the weight of evidence for treatment efficacy lies. Two such systematic reviews have been published in recent years (3, 4). The earlier review was restricted to pharmacologic and nutraceutical therapies (3), and the more recent review included pharmacologic and nutraceutical therapies, alternative therapies, functional foods, physical therapies, surgery, and weight control (4). *Both reviews indicated that the most effective therapies for OA are NSAIDs.* This is supported by evidence in the human literature. Given that effective pain control is central to effective management of OA pain and that NSAIDs have the greatest weight of evidence supporting predictable analgesic effects, it is important to understand how to prescribe NSAIDs to maximize their benefits and minimize their risks.

NSAIDS: MAXIMIZING THE BENEFITS; MINIMIZING THE RISKS

Maximizing the Benefits

NSAIDs are among the most commonly used classes of pharmaceutical in canine practice. Generally, the term *NSAID* is restricted to drugs that inhibit one or more steps in the metabolism of the arachidonic acid cascade, primarily through inhibition of cyclooxygenase (COX) enzymes 1 or 2, but are not steroids. The mechanism of action of some of these drugs is not completely explained by inhibition of arachidonic acid metabolism. In general, NSAIDs are rapidly and predictably effective against OA pain. They can be associated with side effects in a few patients. Much has been written in the veterinary literature on how to minimize these effects (5–9).

The benefit of NSAIDs can be maximized by using them:
- Early in the disease process
- As part of a multimodal treatment plan
- Consistently on a long-term basis rather than as-needed.

Early Treatment with NSAIDS

Often, the clinical approach to a young or middle-aged dog with OA pain is to avoid NSAIDs, the rationale being that the practitioner wants to "save the use of NSAIDs for later, and not have a dog on NSAIDs for the whole of its life." This is a flawed and rather naive approach. If pain is not alleviated, adverse effects on the musculoskeletal system occur (muscle wasting; decreased muscle, ligament, and tendon health), leading to decreased joint support, and increased pain—and continuation of the downward cycle. Thus, *predictable pain relief prevents early deterioration of the musculoskeletal system.* However, NSAIDs (that provide predictable pain relief) usually do not have to be used for the rest of the dog's life. Use of NSAIDs that extends for several months allows increased exercise and weight control or reduction, and these two factors can result in significant and sufficient pain relief to allow the NSAIDs to be discontinued.

Multimodal Therapy

Multimodal therapy for OA pain has been much discussed and promoted through various venues in small animal medicine. Initially, "multimodal" referred to multiple drug treatments, but with the increasing interest in rehabilitation therapy and lifestyle factors (exercise, weight, and dietary management), these have also been embraced in the multimodal management approach.

The basis for suggesting a multimodal drug approach to treat chronic pain stems from the recent understanding of the changes induced in the central nervous system as a result of the constant input of noxious signals from the periphery. Pain transmission involves many pathways, mechanisms, and transmitter systems (10–12). Therefore, it is unlikely that a single class of analgesic, whatever the dose, or nondrug therapy is going to provide complete analgesia. Clinical experience confirms this. However, there is as yet very limited published scientific evidence that multimodal drug therapy is more beneficial than monomodal therapy in veterinary OA patients. For some drugs, such as tramadol, gabapentin, and amitriptyline, there is no evidence of an analgesic effect in canine OA. Additionally, there is almost no information on toxicity when the drugs are used alone or combined with each other or NSAIDs. Yet these drugs, such

as tramadol, are used under the assumption they are safe both alone and combined with NSAIDs. A recent study in humans found that tramadol use before admission in patients hospitalized for treatment of peptic ulcer was associated with a greater risk for mortality than NSAID use before admission. Mortality was 2.02- and 1.41-fold higher in these groups of patients, respectively, than in patients who used neither tramadol nor NSAIDs (13). The study's authors suggest that this may be because tramadol can mask the visceral pain of gastrointestinal irritation and perforation. However, a recent study evaluating the analgesic effects of various doses of rofecoxib and tramadol, both alone and combined, found that the most analgesic combination of tramadol and rofecoxib caused gastric injury in rats that was more severe than that with either drug alone (14). Although it is not known whether the combination of NSAIDs and tramadol in dogs results in greater severity or incidence of gastrointestinal lesions than either drug alone, collectively these data suggest the need for caution when using a multimodal approach.

Currently, the only scientific evidence that supports multimodal drug therapy is one study evaluating the addition of amantadine to the treatment regimen of dogs with pain that was not completely alleviated by an NSAID (15). It is important to note that this evidence points to the benefit of the *addition of an adjunctive drug to an NSAID treatment regimen where the NSAID was not providing full or sufficient pain relief.* It is likely that in this study, dogs with central sensitization were selected for additional treatment. It is unlikely that pain relief from adjunctive drugs alone, or even multiple drugs, will be adequate. Under some circumstances (dogs that are intolerant of NSAIDs, or in which NSAIDs are considered too much of a risk), adjunctive drugs are used alone, but this should be an exception.

Similarly, there is little evidence of a beneficial effect of a multimodal approach combining drug and nondrug therapies. However, there is strong clinical support for combining the therapies of diet modulation (quantity and type), exercise, and weight management with appropriate NSAID therapy.

Long-Term Therapy

There is evidence that joint pain results in the development of central sensitization (16, 17), which is one of the mechanisms leading to increased pain. Further, it has been demonstrated that the COX enzymes play a role in central sensitization (18, 19) and that COX inhibitors can prevent the establishment of central sensitization (19). If a reduction in central sensitization occurred over time with continuous NSAID therapy, pain perception should be progressively reduced. According to a growing body of evidence, central sensitization can actually drive the progression of disease in the periphery (joints), and downward modulation of central sensitization can result in decreased joint pathology (20, 21). In addition, a direct effect of NSAIDs at the level of the joint may reduce disease progression (22, 23). One such mechanism is via the prevention of nitrous oxide (NO)–induced cell death. Several studies have shown that OA cartilage has a higher number of apoptotic chondrocytes than does normal cartilage in animal models and humans. The presence of NO may be an important component in the pathogenesis of OA—it is produced in large amounts by chondrocytes upon proinflammatory cytokine stimulation. Selective inhibition of COX-2 significantly inhibited NO-induced cell death (24). *Several lines of evidence suggest potential theoretical benefits of continuous versus intermittent NSAID analgesic therapy in OA*. A recent review aimed to collate all the information on long-term (defined as greater than 28 days) NSAID therapy and to evaluate the evidence on the safety and efficacy of long-term NSAIDs for treatment of canine OA in the veterinary literature. Secondary aims were to evaluate the evidence for progressive decreases in pain, or progressive tolerance (increase in pain) over time; to evaluate the evidence for altered disease progression with long-term continuous use; and to evaluate the evidence for an increase (or decrease) in the incidence of adverse events with long-term NSAID use. Although not all of the questions could be answered due to a lack of information in the literature, this careful review found that *longer-term (≥28 days) use of NSAIDs, compared with short-term use, clearly resulted in progressively reduced pain and increased function* (**Box 3**). It is not known whether this benefit is the result of peripheral or central changes in pain processing, or a progressive functional improvement due to increased muscle strength and range of motion from the greater mobility resulting from initial pain relief.

Box 3. Abstract of a Recent Review That Evaluated Whether Longer-Term Use of NSAIDs in Dogs with OA-Associated Pain Was Beneficial

The published, peer-reviewed literature was systematically searched for information on the safety and efficacy of long-term (defined as ≥28 days of continuous therapy) NSAID use in the treatment of canine osteoarthritis. Online databases were reviewed in June 2008, and papers were selected based on their relevance. Fifteen papers were identified and evaluated. Six of seven papers indicated a benefit of long-term treatment over short-term treatment in terms of reduced clinical signs and lameness; one study showed no benefit. Fourteen papers evaluated safety with calculated experimental (adverse) event rates between 0 and 0.31, but there was no correlation between study length and adverse event rates (rs = –0.109; $P = 0.793$). The balance of evidence for the efficacy of NSAIDs supports longer-term use of these agents for increased clinical effect. There is no indication in the literature that such an approach is associated with reduced safety, although robust data on the safety of long-term NSAID use are lacking in large numbers of dogs.

Innes JF, Clayton J, Lascelles BD. Review of the safety and efficacy of long-term NSAID use in the treatment of canine osteoarthritis. Vet Rec. 2010;166:226-230.

Minimizing the Risk

Despite proven efficacy in canine OA, the adverse effects have been well-documented (8, 9, 25, 26). Recognition of these effects has led to the suggested clinical approach that the dose be reduced over time (8); although recent evidence (**Box 3**) indicates that long-term use of NSAIDs is not associated with increased adverse events. However, dose reduction is often used clinically and is achieved either by titrating the total daily dose administered or by reducing the frequency of administration. There is no information on whether this approach decreases adverse events. In addition, it is not fully understood whether such downward dose reduction is associated with maintained efficacy. In a study in humans of continuous versus intermittent use of celecoxib, more flare-ups occurred in the intermittent-use group (27). A recent study performed by the author compared continuous full-dose meloxicam with accurately titrated decreasing doses of meloxicam over a period of 112 days (28). This study found dose reduction to be a less effective way to control pain than maintained dosing. However, dose reduction of an NSAID with maintained efficacy (using objective and blinded subjective outcome measures) was possible in some dogs, using accurate, progressive dose reduction with an easily titrated liquid formulation. The success of the dose reduction approach seemed to be dependent on the individual, and there did not seem to be any way to predict whether a dog would respond positively to dose reduction. Although the study was not powered to evaluate the frequency of adverse events between the two groups, there was no difference in the number of such events.

There is a strong belief that the adverse events of NSAID administration may be more closely related to an individual animal's inherent response to NSAIDs than the duration of administration. We cannot currently predict which animals will be intolerant, but the rapidly advancing area of pharmacogenomics might provide some practical clinical guidance in the future.

What is clear is that the way in which we as practitioners use NSAIDs significantly affects whether adverse events occur. This is the area in which we can have the greatest impact in minimizing the risks of these drugs. The most important aspects in this regard are the following:

- Concurrent medication
- Appropriate dosing
- Patient selection and screening for risk factors
- Communication with owners.

Concurrent Medication

It is important to fully determine what other drugs an animal is receiving and to consider possible interactions. A good history will determine this. Some medications may not have been prescribed by your veterinary practice. For example, many owners will use aspirin not realizing it is an NSAID, particularly if they themselves are on a regimen of low-dose aspirin and an NSAID. Review of information on adverse events called into the U.S. Food and Drug Administration (FDA) (29) and review of published data (25) indicate that *many cases of suspected NSAID-associated adverse events have involved concurrent use of a steroid or another NSAID.* The potential adverse effects of this combination are

completely avoidable by us, the prescribing veterinarians. However, the owners need to be questioned appropriately, and the medical records reviewed. Recent marketing surveys have indicated that up to 30% of pet owners may be using aspirin. The clear evidence that buffered aspirin is obviously associated with greater gastrointestinal side effects in dogs than FDA-approved NSAIDs is often forgotten (30, 31). Owners may also not consider aspirin to be an NSAID if they are asked if their pet has been on an NSAID because of the way aspirin is marketed to humans.

Another area in which caution is advised is concurrent use of topical steroid–containing preparations and NSAIDs. Topical steroids are present in many commercial otic and skin products (creams, sprays, ointments). The potency of the steroid depends on its inherent anti-inflammatory quotient, as well as on the drug concentration and vehicle used in the product. Relative potencies (relative potencies are in parentheses) of various steroids compared with hydrocortisone are hydrocortisone, prednisolone, triamcinolone, isoflupredone, dexamethasone (25), betamethasone (25), and fluocinolone (100). Systemic absorption, with suppression of the hypothalamic–pituitary–adrenal axis, probably increases with greater potency. A recent study of the degree of adrenocortical suppression after clinical use of various preparations (Mometamax [mometasone], DVMax [betamethasone], Panolog [triamcinolone], and Tresaderm [dexamethasone]) found suppression of the adrenocortical axis in 0%, 9%, 17%, and 50% of dogs after 7 days of treatment, respectively. That adrenocortical suppression was measurable suggests significant systemic absorption. It should be presumed that the potential for systemic absorption of the steroid exists with all of these preparations. *There is no information on the safety of concurrent use of any topical steroid-containing preparation and NSAIDs.* Systemically administered steroids have been shown to cause additive gastrointestinal adverse effects when combined with NSAIDs. Endoscopically visible lesions increased in severity when prednisone was given with the NSAID flunixin meglumine (32) and dexamethasone given with meloxicam (33). Recently, a study evaluated coadministration of prednisolone (2.3 mg/kg daily) compared with prednisolone (2.3 mg/kg daily) and ultra–low-dose aspirin (0.5 mg/kg daily) (34). Although the gastric lesions did not differ statistically between groups, more days of diarrhea occurred in the combined medication group, illustrating the adverse effects of combining even low doses of NSAIDs with steroids.

Appropriate Dosing

Higher-than-approved doses of NSAIDs should not be used—they are not more effective and decrease the safety margin. NSAIDs should be dosed on lean body mass, which reduces the incidence of side effects.

Patient Selection and Screening for Risk Factors

Appropriate screening and patient factors that should be identified are summarized in **Box 4**. Veterinarians are often faced with the dilemma of deciding what to do in cases where elevated liver enzymes are detected before NSAID therapy is started, with a major concern being the potential for NSAID-induced liver toxicity. Already-existing liver dysfunction, which will increase the likelihood of NSAID-related adverse effects, is also a concern. All NSAIDs are metabolized by the liver, and hepatoxicity is an idiosyncratic event that can occur with any member of this class, regardless of COX-selectivity. The extensive experience with NSAIDs in human medicine provides the veterinary practitioner with a useful comparison with what has been reported and can therefore be anticipated. Reports of NSAID-associated hepatotoxicity in human patients are considered rare but inevitable due to the high level of use. An incidence of 1–10 per 100,000 persons has been reported in Australia (35), whereas a large European epidemiologic study (n = 400,000 patients) found that NSAIDs were associated with a 1.3- to 1.9-fold increase in the incidence of all hepatopathies (36). Increased occurrence is associated with concurrent liver disease (e.g., hepatitis, cirrhosis) and advanced patient age (>50 years) (35, 37), usually within 12 weeks of the start of therapy (35, 38, 39). Human NSAID-associated hepatopathies have been associated with nonselective, selective, and preferential COX-2 inhibitors alike (37, 39, 40).

Box 4. Screening and Patient Factors for Evaluation of OA Risk

Screening and monitoring are very important to identify higher-risk patients and thus to ensure risks can be minimized when possible. Adverse event reports related to NSAIDs may be

disproportionately associated with older animals, so it is recommended that dogs 6 years and older be carefully evaluated for concurrent disease and overall suitability. Although not comprehensive, a suitable practical approach to screening is outlined below. In some cases, after full consultation with the owner, a decision will be made to use NSAIDs despite the presence of a risk factor. This is usually done after a discussion of risks and benefits. In such cases, more frequent and targeted monitoring can be performed.

1. *History and physical examination*: A thorough history and physical examination, including identification of any previously administered medications and the animal's reaction to them, enable assessment of the patient's overall health and the possibility of drug interactions.

2. *Hematologic and clinical chemistry evaluations*: Baseline: It is important to determine hematologic and serum biochemistry and urinalysis baseline values before initiating treatment and periodically thereafter for any animal receiving long-term therapy with NSAIDs (or any medication, for that matter). Abnormal baseline values should be appropriately investigated. For example, significantly increased liver enzymes should be followed by measurement of bile acids to evaluate liver function. The author considers increased liver enzymes, or an alanine transaminase level more than twice the top end of normal or an alkaline phosphatase more than the 5 times the top end of normal, to be indications for evaluating bile acids (see main text).

3. *Monitoring*: If clinical chemistry levels reveal renal or hepatic compromise, more frequent monitoring is essential if NSAIDs are used. There is no consensus on frequency of monitoring, but the author recommends the following in dogs:

- Baseline blood panel/urinalysis
- Renal and liver panel 2 weeks after initiating NSAID treatment
- Routine blood clinical chemistry panel and urinalysis every 6 to 12 months in young, healthy animals or every 2 to 3 months in older dogs

4. *Identification of preexisting disease*: The baseline clinical chemistry/hematology/urinalysis will help to detect concurrent disease. NSAIDs should be used with caution or not at all in animals with a history of NSAID-associated adverse reactions (although adverse reactions are often individualized and few dogs do not tolerate any NSAID). Other NSAID contraindications include the following:

- Evidence of gastric ulceration (e.g., melena) or GI disorders associated with mucosal damage. Risk factors for GI ulceration include:
  - *History of GI ulceration*: Animals with a history of GI ulceration may be more prone to the toxic GI effects of any NSAID
  - *Geriatric patients*: Older animals may have reduced drug clearance capacity and thus are more susceptible to NSAID toxicity because each dose results in comparatively greater circulating concentrations
  - *Concurrent use of aspirin*
  - *Inadequate wash-out period (i.e., <5–7 days) when switching NSAIDs*: There is no scientific evidence that rapid switching between NSAIDs leads to frequent problems; however, rapid switching is commonly a factor when NSAID toxicity occurs in dogs
  - *Concurrent liver disease*: The exact reasons are unknown, but concurrent liver disease may be due to decreased clearance of circulating levels of gastrin
  - *Renal insufficiency*: Circulating blood urea nitrogen can lead to GI ulceration; animals with renal impairment may have increased circulating levels of gastrin

- ➢ *Mast cell neoplasia*: Significant numbers of animals with mast cell neoplasia have concurrent GI ulceration

- *Renal insufficiency*: Documented by such findings as increased renal biochemical measures, lack of concentrating ability, and/or abnormal urine protein–creatinine ratios

- *Patients with reduced hepatic function*: Most readily documented by increased bile acids. Increased liver enzymes in the absence of decreased liver function is not a risk factor for NSAID-associated liver toxicity

- *Conditions associated with low effective circulating volume*: Congestive heart failure, ascites, use of diuretics

- *Pregnant animals*

Adverse drug event reports submitted to the FDA indicate that carprofen, the most widely used veterinary NSAID, has a hepatotoxicity incidence of less than 0.05%, with hepatic dysfunction occurring in less than 0.02% of treated dogs. These rates, involving a sizable population of treated dogs, are probably similar to the reported incidence of other NSAIDs. Three- to 4-fold increases in hepatic enzymes above the normal range concurrent with NSAID treatment have been noted, and resolution of clinical signs and enzyme values after treatment discontinuation confirms hepatotoxicity.

In dogs with elevated liver enzymes before NSAID treatment, relatively more frequent liver enzyme monitoring may be warranted, although there is currently no evidence to suggest that increased liver enzymes per se are a risk factor for hepatopathy. Although the incidence of NSAID-associated hepatotoxicity is low, the possibility should not be ignored. There is a growing consensus that baseline alanine aminotransferase and aspartate aminotransferase values should be obtained before long-term NSAID therapy is started and followed by retesting 4–6 weeks later. Trends, as opposed to absolute values, should be evaluated.

In dogs whose liver enzymes are elevated before NSAID treatment, when to further investigate liver function needs to be decided. Liver function is the most important factor to be evaluated during NSAID treatment. The author considers historic evidence of increasing liver enzymes, alanine aminotransferase values two or more times the upper end of the normal range or alkaline phosphatase levels 5 or more times the upper end of normal, to be indications for measurement of bile acids. Measuring pre- and postprandial levels is probably the best in-clinic test to evaluate liver function. A study has recently suggested urine evaluation to measure bile acids and thus liver function (41). In that study, the urinary ratios of nonsulfated bile acids to creatinine, and urine sulfated bile acids plus unsulfated acids to creatinine, had the best diagnostic performance of the urine bile acid tests. Each had a substantially higher specificity, slightly higher positive predictive value, slightly lower negative predictive value, and lower sensitivity than the serum bile acid test. The urine bile acid-to-creatinine values were positively correlated with serum bile acid values. These data suggest that urinary measurement of bile acids has clinical utility, but sensitivity is best with the serum bile acid test.

If decreased hepatic function is discovered, NSAIDs should not be used or should be used with extreme caution. This is because hepatic disease leads to the following:

- Increased risk for gastrointestinal ulceration; the exact reasons are not known, but decreased excretion of gastrin and decreased bile acids in the intestinal tract may play a role

- Decreased metabolism of NSAIDs (and other drugs), leading to a relative systemic overdose with repeated dosing.

Communication with Owners

When NSAIDs are prescribed, clients must be informed of the potential adverse effects that are common to all drugs in this class. In a review of the types of adverse events reported to the FDA (29), 23% of owners stated that their veterinarian had never discussed any potential adverse effects and 22% stated that their veterinarian did not give them the client information sheet. Pet owners need to be told about potential side effects and their associated

clinical signs. Client information sheets can be obtained from the manufacturer of the respective NSAID. That NSAID treatment should be discontinued immediately and the animal brought to the clinic if there is any suspicion of adverse effects must be emphasized during client counseling. Vomiting should be taken particularly seriously—it has been the most common, or first, finding associated with gastrointestinal ulceration in several studies (25, 42, 43). However, the incidence of vomiting and the sensitivity of this sign as a clinical indicator of more serious problems are not known. Clients should also be counseled on what drugs should not be given concurrently with NSAIDs, such as aspirin, steroids, and topical steroid-containing sprays and creams.

The FDA (29) has reported that most adverse events occur within the first 14–30 days after administration initiation; clients should be counseled to be especially vigilant during this time. Although there is a lack of evidence that longer administration of an NSAID increases the incidence of side effects, it is nonetheless appropriate to counsel the client that particular lifestyle or health changes may increase the risk for NSAID-related side effects in dogs that are otherwise tolerating them, such as:

- Gastrointestinal irritation occurring from any cause
- Dehydration (such as might occur on a hot day or after a long walk)
- Stress (such as might occur with house moves or family stresses)
- Anesthesia and surgery (cause stress and can place physiologic strain on the kidneys).

The author recommends calling the client 1–2 weeks after the start of NSAID treatment to discuss efficacy and potential side effects and reevaluating the patient 4 weeks after treatment has begun. Good compliance with this request can be obtained by enlisting the client as a full partner in the pet's pain management plan. In this scenario, the veterinarian suggests and initiates a therapeutic program, and the plan is then affirmed or modified based on client feedback. This approach lets the client know that the veterinarian values the owner's insight, which fosters rapport and encourages feedback. Listening to client feedback and taking it seriously will optimize the client's understanding and attention to detail in monitoring side effects. This team approach greatly improves the chances for an optimum treatment outcome when NSAIDs are prescribed. An outline of this approach is provided in **Box 5**.

Box 5. The Team Approach to NSAID Therapy

- When NSAIDs are prescribed, inform clients of potential adverse effects and their clinical signs.
- Dispense the "client information sheets" produced by the NSAID manufacturer.
- Have a member of your staff read through this sheet with the client, pointing out the most common signs of adverse effects (i.e., vomiting).
- Emphasize that NSAID treatment should be discontinued immediately and the animal brought to the clinic if there is any suspicion of adverse effects.
- Emphasize that other NSAIDs and aspirin should not be administered concurrently with the prescribed drug.
- Discuss other medications that the pet is receiving, being careful to ask about any potential NSAIDs or steroids and transdermal/otic/ophthalmic sprays, drops, and creams that contain steroids.
- Enlist the client as a full partner in the pet's pain management plan and indicate that you are interested in and need his or her feedback.
- Ask the client to call in 1 to 2 weeks after the start of NSAID treatment to discuss efficacy and tolerance (despite the request, the practice should call the client).

Schedule an appointment 4 weeks after treatment has begun to discuss efficacy and tolerance.

(Text continues on page 50).

REFERENCES

1. Runge JJ, Biery DN, Lawler DF, et al. The effects of lifetime food restriction on the development of osteoarthritis in

the canine shoulder. Vet Surg. 2008;37:102-107.

2. Smith GK, Paster ER, Powers MY, et al. Lifelong diet restriction and radiographic evidence of osteoarthritis of the hip joint in dogs. JAVMA. 2006;229:690-693.

3. Aragon CL, Hofmeister EH, Budsberg SC. Systematic review of clinical trials of treatments for osteoarthritis in dogs. JAVMA. 2007;230:514-21.

4. Sanderson RO, Beata C, Flipo RM, et al. Systematic review of the management of canine osteoarthritis. Vet Rec. 2009;164:418-424.

5. Johnston SA, Budsberg SC. Nonsteroidal anti-inflammatory drugs and corticosteroids for the management of canine osteoarthritis. Vet Clin North Am Small Anim Pract. 1997;27:841-862.

6. Bergh MS, Budsberg SC. The coxib NSAIDs: potential clinical and pharmacologic importance in veterinary medicine. J Vet Intern Med. 2005;19:633-643.

7. Minimizing the risk factors associated with veterinary NSAIDs. 2004. (Accessed at www.avma.org/onlnews/javma/apr04/040415g.asp.)

8. Lascelles BD, McFarland JM, Swann H. Guidelines for safe and effective use of NSAIDs in dogs. Vet Ther. 2005;6:237-251.

9. Papich MG. An update on nonsteroidal anti-inflammatory drugs (NSAIDs) in small animals. Vet Clin North Am Small Anim Pract. 2008;38:1243-1266.

10. Mannion RJ, Woolf CJ. Pain mechanisms and management: a central perspective. Clin J Pain. 2000;16:S144-156.

11. Muir WW, 3rd, Woolf CJ. Mechanisms of pain and their therapeutic implications. JAVMA. 2001;219:1346-1356.

12. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science. 2000;288:1765-1769.

13. Torring ML, Riis A, Christensen S, et al. Perforated peptic ulcer and short-term mortality among tramadol users. Br J Clin Pharmacol. 2008;65:565-572.

14. Garcia-Hernandez L, Deciga-Campos M, Guevara-Lopez U, Lopez-Munoz FJ. Co-administration of rofecoxib and tramadol results in additive or sub-additive interaction during arthritic nociception in rat. Pharmacol Biochem Behav. 2007;87:331-340.

15. Lascelles BD, Gaynor JS, Smith ES, et al. Amantadine in a multimodal analgesic regimen for alleviation of refractory osteoarthritis pain in dogs. J Vet Intern Med/Am Coll Vet Intern Med. 2008;22:53-59.

16. Menetrey D, Besson JM. Electrophysiological characteristics of dorsal horn cells in rats with cutaneous inflammation resulting from chronic arthritis. Pain. 1982;13:343-364.

17. Neugebauer V, Schaible HG. Evidence for a central component in the sensitization of spinal neurons with joint input during development of acute arthritis in cat's knee. J Neurophysiol. 1990;64:299-311.

18. Samad TA, Moore KA, Sapirstein A, et al. Interleukin-1 beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. Nature. 2001;410:471-475.

19. Veiga APC, Duarte IDG, Avila MN, da Motta PG, Tatsuo M, Francischi JN. Prevention by celecoxib of secondary hyperalgesia induced by formalin in rats. Life Sciences. 2004;75:2807-2817.

20. Sluka KA, Jordan HH, Westlund KN. Reduction in joint swelling and hyperalgesia following posttreatment with a

non-NMDA glutamate-receptor antagonist. Pain. 1994;59:95-100.

21. Fiorentino PM, Tallents RH, Miller JNH, et al. Spinal Interleukin-1 beta in a mouse model of arthritis and joint pain. Arthritis Rheum. 2008;58:3100-3109.

22. Pelletier JP, Lajeunesse D, Hilal G, Jovanovic D, Fernandes JC, MartelPelletier J. Carprofen reduces the structural changes and the abnormal subchondral bone metabolism of experimental osteoarthritis. Osteoarthritis Cart. 1999;7:327-328.

23. Pelletier JP, Boileau C, Brunet J, et al. The inhibition of subchondral bone resorption in the early phase of experimental dog osteoarthritis by licofelone is associated with a reduction of MMP-13 and cathepsin K synthesis. Ann Rheum Dis. 2004;63:145.

24. Jovanovic DV, Mineau F, Notoya K, Reboul P, Martel-Pelletier J, Pelletier JP. Nitric oxide induced cell death in human osteoarthritic synoviocytes is mediated by tyrosine kinase activation and hydrogen peroxide and/or superoxide formation. J Rheumatol. 2002;29:2165-2175.

25. Lascelles BD, Blikslager AT, Fox SM, Reece D. Gastrointestinal tract perforation in dogs treated with a selective cyclooxygenase-2 inhibitor: 29 cases (2002-2003). JAVMA. 2005;227:1112-1117.

26. Innes JF, Clayton J, Lascelles BD. Review of the safety and efficacy of long-term NSAID use in the treatment of canine osteoarthritis. Vet Rec. 2010;166:226-230.

27. Luyten FP, Geusens P, Malaise M, et al. A prospective randomised multicentre study comparing continuous and intermittent treatment with celecoxib in patients with osteoarthritis of the knee or hip. Ann Rheum Dis. 2007;66:99-106.

28. Wernham BGJ, Trumpatori B, Hash J,et al. Dose titration of meloxicam in dogs with OA-associated pain and mobility impairment. J VetIntern Med. In press.

29. Hampshire VA, Doddy FM, Post LO, et al. Adverse drug event reports at the United States Food And Drug Administration Center for Veterinary Medicine. JAVMA. 2004;225:533-536.

30. Reimer ME, Johnston SA, Leib MS, et al. The gastroduodenal effects of buffered aspirin, carprofen, and etodolac in healthy dogs. J Vet Intern Med. 1999;13:472-477.

31. Sennello KA, Leib MS. Effects of deracoxib or buffered aspirin on the gastric mucosa of healthy dogs. J Vet Intern Med. 2006;20:1291-1296.

32. Dow SW, Rosychuk RA, McChesney AE, Curtis CR. Effects of flunixin and flunixin plus prednisone on the gastrointestinal tract of dogs. Am J Vet Res. 1990;51:1131-1138.

33. Boston SE, Moens NM, Kruth SA, Southorn EP. Endoscopic evaluation of the gastroduodenal mucosa to determine the safety of short-term concurrent administration of meloxicam and dexamethasone in healthy dogs. Am J Vet Res. 2003;64:1369-1375.

34. Heather Graham A, Leib MS. Effects of prednisone alone or prednisone with ultralow-dose aspirin on the gastroduodenal mucosa of healthy dogs. J Vet Intern Med. 2009;23:482-487.

35. Teoh NC, Farrell GC. Hepatotoxicity associated with non-steroidal anti-inflammatory drugs. Clin Liver Dis. 2003;7:401-413.

36. Traversa G, Bianchi C, Da Cas R, Abraha I, Menniti-Ippolito F, Venegoni M. Cohort study of hepatotoxicity

associated with nimesulide and other non-steroidal anti-inflammatory drugs. BMJ. 2003;327:18-22.

37. Alegria P, Lebre L, Chagas C. Celecoxib-induced cholestatic hepatotoxicity in a patient with cirrhosis. Ann Intern Med. 2002;137:75.

38. O'Connor N, Dargan PI, Jones AL. Hepatocellular damage from non-steroidal anti-inflammatory drugs. QJM 2003;96:787-791.

39. Galan MV, Gordon SC, Silverman AL. Celecoxib-induced cholestatic hepatitis. Ann Intern Med. 2001;134:254.

40. Maddrey WC, Maurath CJ, Verburg KM, Geis GS. The hepatic safety and tolerability of the novel cyclooxygenase-2 inhibitor celecoxib. Am J Ther. 2000;7:153-158.

41. Balkman CE, Center SA, Randolph JF, et al. Evaluation of urine sulfated and nonsulfated bile acids as a diagnostic test for liver disease in dogs. JAVMA. 2003;222:1368-1375.

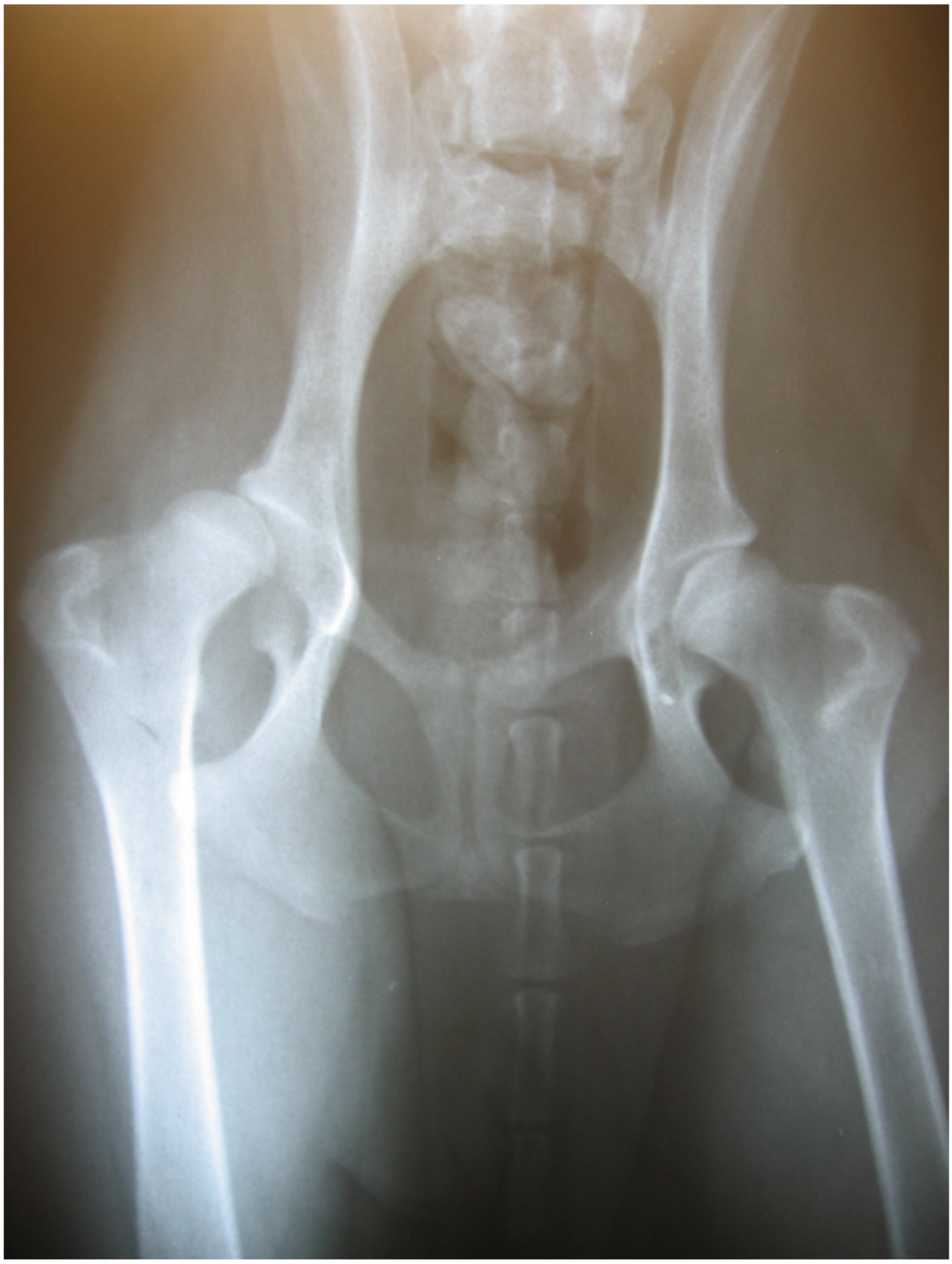
42. Neiger R. NSAID-induced gastrointestinal adverse effects in dogs--can we avoid them? J Vet Intern Med. 2003;17:259-261.

43. Stanton ME, Bright RM. Gastroduodenal ulceration in dogs. Retrospective study of 43 cases and literature review. J Vet Intern Med, 1989;3:238-244.

CASE REPORT: SPAYED FEMALE ENGLISH SETTER, 16 KG

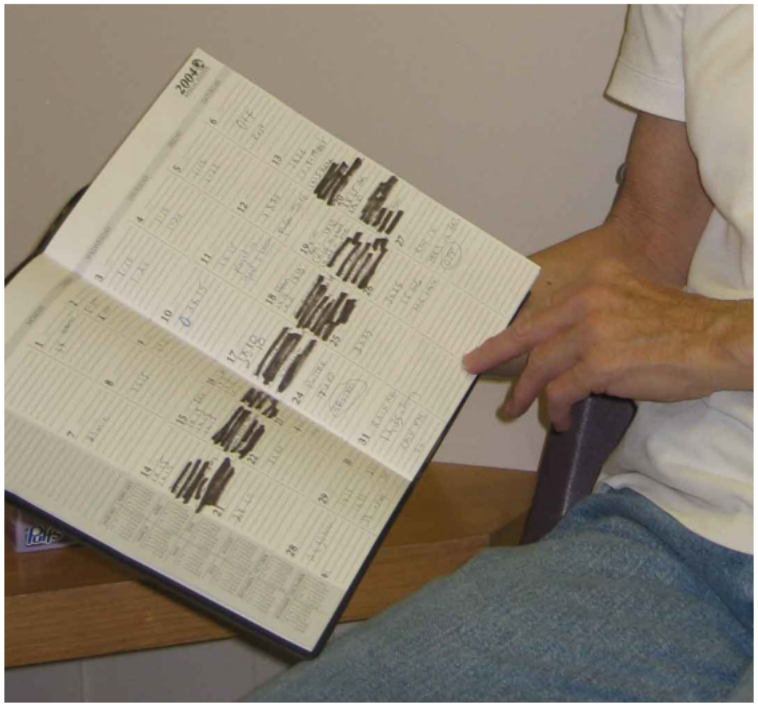
This case presented at the age of 14 months to the Integrated Pain Management Clinic, with a history of limping and reluctance to play for the past 5 months. The owner reported that the right hip seemed to luxate occasionally, and the dog often slipped in association with this apparent luxation during activities.

Examination revealed bilateral hip dysplasia with associated pain and dramatically reduced muscle mass on both hindlimbs. The dog ambulated with a hunched appearance. Radiographs showed bilateral hip dysplasia, radiographically worse on the right (see **radiographs, February 2004**). CBC and blood chemistry were normal.



February 2004. The ventrodorsal radiograph of the pelvis shows bilateral hip dysplasia. The left side is almost completely luxated. Both sides had significant laxity on palpation.

Early treatment consisted of:
• Rest and NSAID (carprofen, 25 mg BID) and tramadol (50 BID) for 5 days
• Following this, increasing leash exercise over an 8-week period; carprofen 25 mg BID for 8 weeks.
A phone call after 2 weeks indicated some improvement, and no side effects. The owner was asked to keep a diary of treatments administered, and exercise durations (see **diary image**)



Diary of therapy. The owners were fully engaged in the treatment of their pet, keeping track of medication and exercise in the early part of the treatment regimen. Engaging the owner in the early phases is critical. Asking owners to keep diaries and reviewing them at rechecks can keep them engaged owners and helps the veterinarian determine how closely the management plan is being followed.

Reevaluation April 2004:

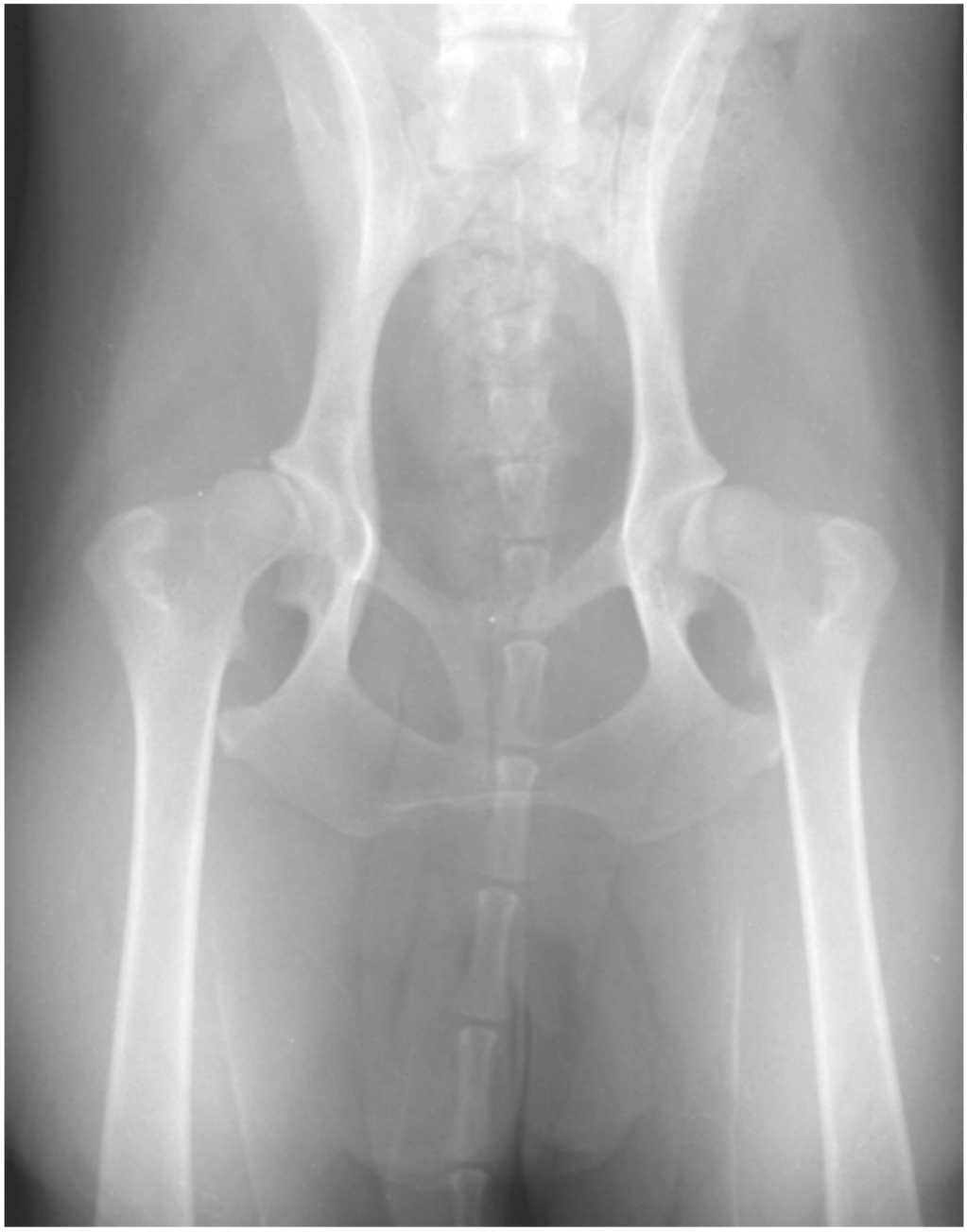
- CBC and blood chemistry normal
- Current level of exercise was 30 minutes leash walk twice daily
- Gait and function had improved, and pain decreased
- Plan:
  - ➢Continue carprofen (25 mg BID)
  - ➢Start dietary supplementation with glucosamine-chondroitin sulfate and fish oil
  - ➢Initiate short runs every couple of days

Reevaluation June 2004:

- CBC and blood chemistry normal
- No NSAID-associated adverse events
- Currently exercising 30 minutes leash walk twice daily and running 10 miles a week
- Dietary supplements tolerated well
- Further improvement in gait and function, and decrease in pain
- Hips appear to be much less lax on palpation
- Plan:
  - ➢Continue carprofen (25 mg SID)
  - ➢Continue dietary supplementation with glucosamine-chondroitin sulfate and fish oil
  - ➢Continue exercise regimen, gradually increasing the amount of running if possible

Reevaluation December 2004

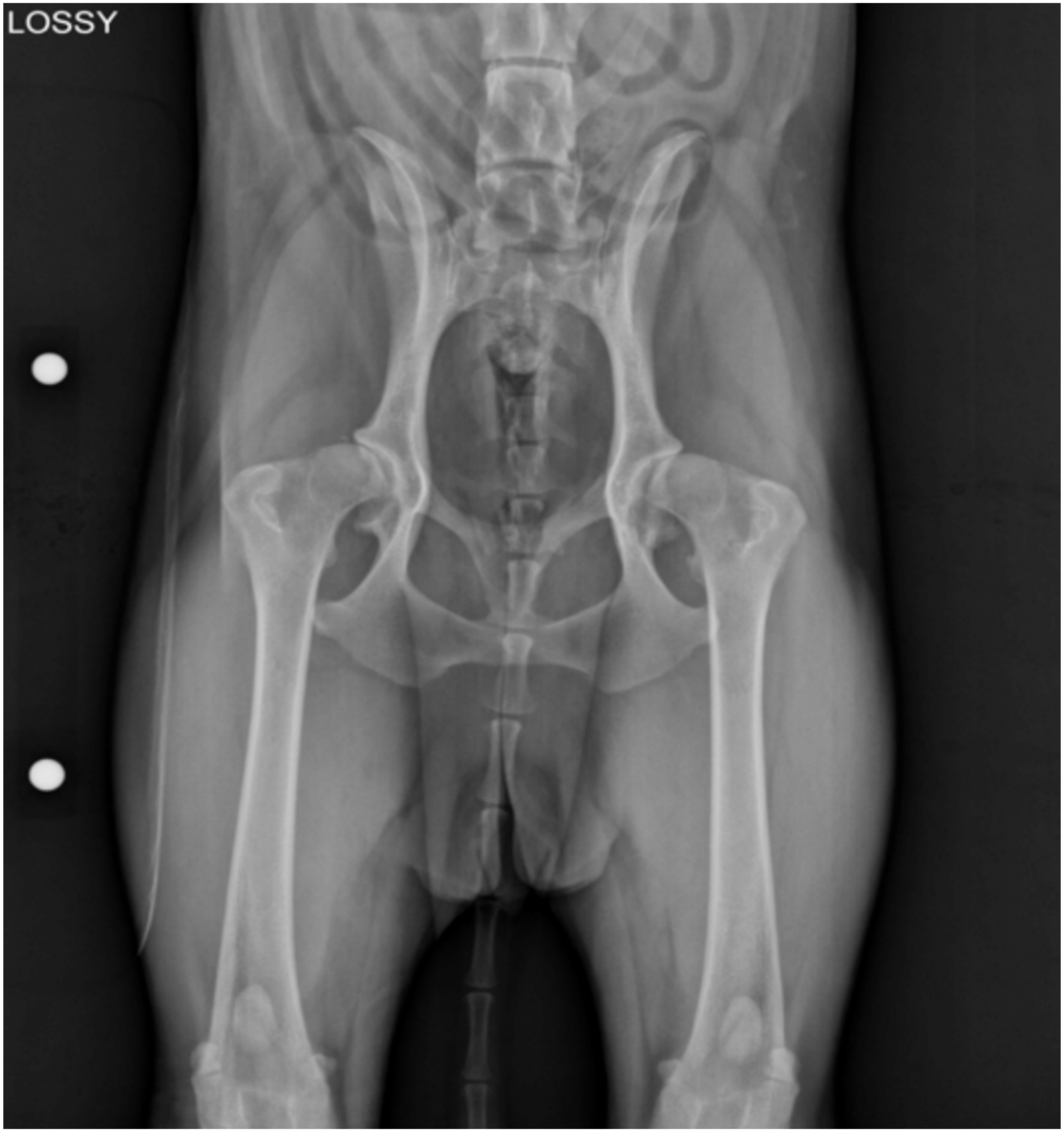
- Had not received NSAIDs for the previous month
- Currently exercising 30 minutes leash walk twice daily and running 20 miles a week; weight maintained at 16 kg
- Gait and function optimal; no pain on manipulation
- Radiographs suggest improved coxofemoral articulation (see **radiographs, December 2004**)



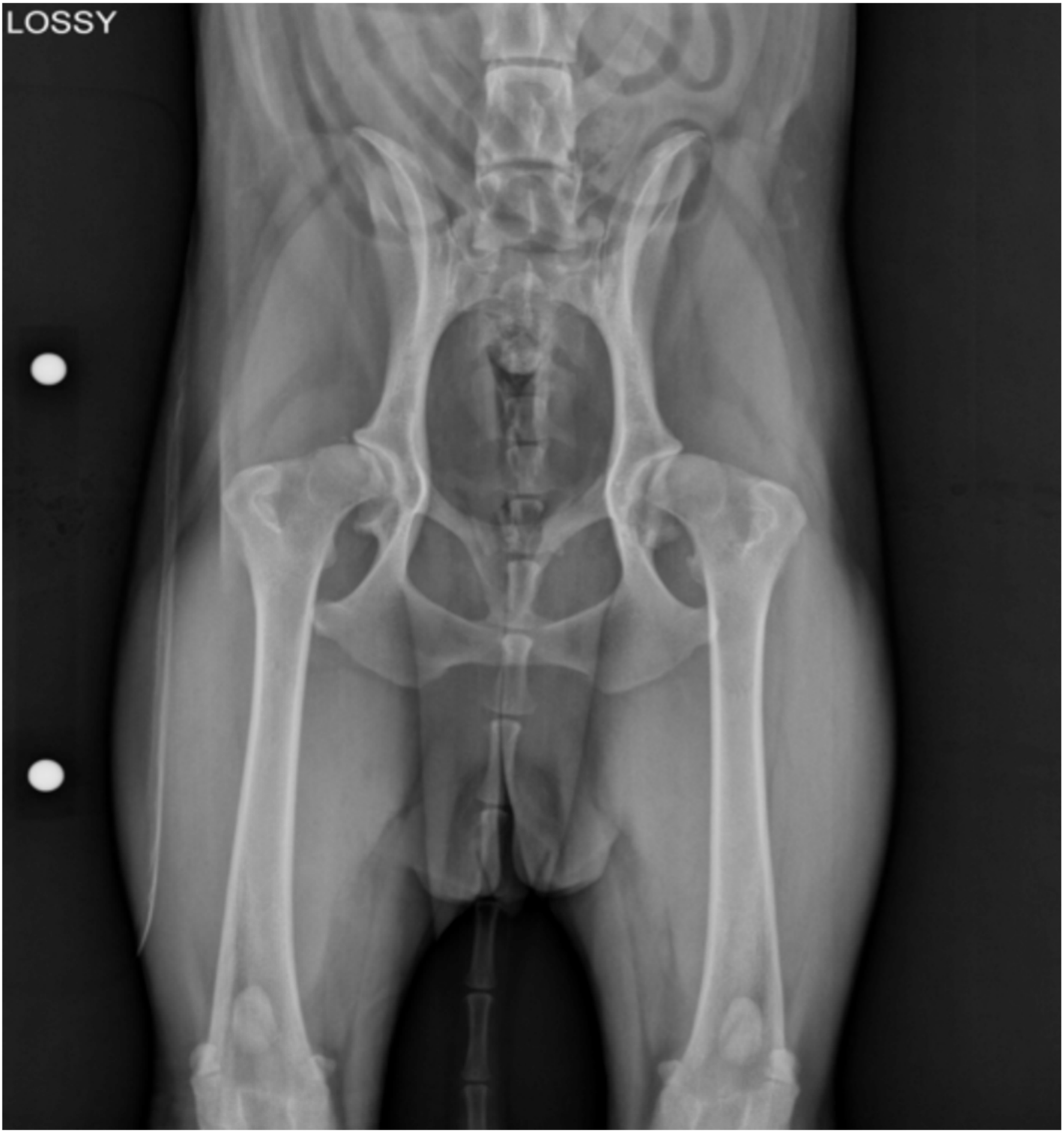
December 2004. Ventrodorsal radiographs taken after 10 months of treatment seem to suggest decreased subluxation, and minimal progression of OA.

- Plan:
  - ➢Continue dietary supplementation with glucosamine-chondroitin sulphate and fish oil
  - ➢Continue exercise regimen

Since December 2004, the dog has not received any NSAIDs and is functioning normally. Muscle mass and range of motion are normal. Careful attention to bodyweight has allowed weight to be maintained at 16 kg, despite occasional temporary increases. The dog still receives glucosamine-chondroitin sulfate and fish oil supplementation and maintains a steady exercise regimen (20–30 minutes leash walk twice daily and 12–15 miles running each week). Follow-up radiographs showed minimal worsening of OA (see **radiographs, August 2006** and **August 2007**). It is expected that in the future, NSAIDs may be required for pain associated with worsening OA. It is hoped that lifestyle management (weight and exercise) will minimize progression of OA and the associated pain.



August 2006. The dog was treated conservatively for severe hip dysplasia and pain. A combination of effective, long-term analgesia (9 months) and increasing exercise was used, with a transition through a dose reduction of NSAIDs. She was eventually maintained in optimal condition through lifestyle management, including weight control and nutritional supplementation



August 2007. Follow-up ventrodorsal radiographs of the pelvis show minimal change in OA. Palpation at this time indicated very little palpable laxity, probably due to the increased soft tissue support resulting from regular exercise.

Small Changes, Big Results – Rethinking Your Anesthetic Protocols

Andre Shih, DVM. Diplomate, ACVA

ABSTRACT

All anesthetic drugs can cause some degree of cardiorespiratory depression. This is of greater concern in patients that already have an underlying disease. This article will discuss some anesthetic options for challenging cases, focusing on geriatric patients, patients with cardiac disease, patients with polytrauma, and cats with lower urinary tract obstruction. Regardless of the case, when anesthesia is planned it is important to systematically analyze all disease processes separately and to consider their possible interaction with the anesthetic agents. It is important to determine whether the planned procedure will result in complications, such as hemorrhage, sympathetic stimulation, pain, or cardiorespiratory depression.

POINTS TO PUT A FINGER ON

- Geriatric patients usually have lower organ reserve capacity; the main presurgical goals for geriatric patients are to decrease stress and provide good analgesia.
- The acute tissue injury caused by trauma triggers pain and activates the hypothalamic–pituitary–adrenal axis; the stress response that occurs after multiple traumatic injuries accounts for a high percentage of the mortality seen in trauma patients.
- Multimodal analgesia involves a combination of two or more agents from different drug classes to provide either an additive or a synergistic effect; this protocol can potentially lower the dose of each drug, thereby reducing the possibility of undesirable side effects.
- During surgery, monitoring is essential to ensure rapid diagnosis and timely treatment of cardiorespiratory complications.
- It is speculated that a good percentage of anesthesia deaths in routine cases may be secondary to undiagnosed cardiac disease.
- For animals with a diagnosis of dynamic left ventricular outflow obstruction, an intravenous combination of opioids and low-dose dexmedetomidine should yield effective sedation.

ANESTHESIA FOR GERIATRIC PATIENTS

With improvements in both husbandry and veterinary care, there has been an increase in the life expectancy of our pets. Anesthesia of geriatric patients is not very different from anesthesia of younger patients; however, perioperative management of the geriatric patient requires knowledge of the physiologic changes associated with aging and their relationship with the effects of the drugs being administered (1). The term "geriatric" cannot be defined as animals of a set age range, because the life expectancy of dogs varies depending on breed and size. Giant breeds have a shorter life expectancy than smaller breeds. With this in mind, 70%–80% of the anticipated natural life span has been suggested as the beginning of the geriatric phase.

The effect of age on perioperative morbidity is related to comorbid conditions and decreased physiologic reserve of the various organ systems. Cardiovascular physiology changes significantly as the patient ages. Myocardial contractility remains relatively unchanged until late in life, but there is a decrease in cardiac reserve capacity and ventricular compliance as well as blunted beta-receptor responsiveness (1). The geriatric patient therefore cannot handle abrupt changes in preload and afterload as efficiently as a younger animal. A relatively small decrease in venous return (i.e., dehydration, hypovolemia, or hemorrhage) can significantly reduce stroke volume (2). On the other hand, aggressive and rapid fluid administration can easily lead to congestive heart failure and pulmonary edema.

Age is also associated with decreased pulmonary compliance and decreased functional residual capacity of the lungs. This is due to a decrease in pulmonary elasticity and ossification of the costochondral junctions. The closing capacity of the distal alveoli is greatly reduced, making geriatric patients more prone to ventilation–perfusion mismatch. Hypoxemia is more likely to occur after sedation or anesthesia without supplemental oxygen therapy (2).

Neurotransmitter activity of the geriatric nervous system is usually reduced, which increases sensitivity to anesthetic drugs. Geriatric patients tend to have reduced renal and hepatic perfusion, which partially explains their decreased ability to clear drugs and the increased duration of anesthetic agents administered.

Premedication

Preoperative evaluation of the geriatric patient is typically more complicated than that of the younger patient (3). Particular attention should be given to auscultation of the heart and lungs. Complete blood work, including hematocrit, plasma protein, and renal and hepatic functional panel, should be considered the minimum for preanesthetic laboratory testing in this age group (3).

The main concern during premedication is to decrease stress and provide good analgesia. Age by itself minimally changes anesthetic requirements—the increase in anesthesia-related morbidity is usually related to concurrent age-related diseases. Degenerative disease, decreased organ reserve capacity, and neoplasia can significantly influence plasma protein concentration and renal function, influencing the free fraction, potency, and duration of anesthetic drugs (2). Geriatric patients generally require less anesthetic agent for equivalent effect. Depending on comorbidity, some drugs, including xylazine, dexmedetomidine, and acepromazine, are best avoided in geriatric patients. Opioids are a good choice for premedication. They provide adequate sedation in most animals, with minimal cardiovascular and respiratory effects. Opioids reduce the amount of induction and inhalant anesthetic required (4).

Induction

One of the main concerns during induction is to avoid stress and myocardial depression (4). The response of the older patient to surgical stress is often unpredictable. Extra care must be taken to ensure good analgesia during the perioperative period. Most short-acting intravenous induction agents are suitable for geriatric patients. These include propofol, thiopental, dissociative anesthetics (ketamine and telazol), and etomidate. It is preferable to reduce the dose of induction agent (10%–30%) and administer it slowly to compensate for pharmacodynamic changes due to age-related disease. Supplemental oxygenation should be available in all cases that require heavy sedation or general anesthesia.

Maintenance

Inhalant agents offer a good option for maintenance of anesthesia. It is important to remember that the minimum alveolar concentration for inhaled anesthetics is 30% less in older dogs than in younger ones. Whenever possible, local anesthesia should be used for analgesia to reduce the amount of anesthetic necessary. Intensive monitoring during anesthesia is essential to ensure rapid diagnosis and timely treatment of cardiorespiratory complications. The veterinarian should be able to monitor patient oxygen saturation, blood pressure, heart rate, and end-tidal carbon dioxide.

Recovery and Postanesthetic Management

Recovery should take place in a quiet area (5). It is advisable to monitor the patient for about 3 hours after general

anesthesia because anesthesia-related fatalities most commonly occur during this period (6). Appropriate analgesics should be administered. Geriatric patients may have comorbid conditions that make them prone to chronic (pathologic) pain syndrome. Opioids can lead to excessive sedation, which is not always advantageous during the postoperative period (2). Nonsteroidal anti-inflammatory drugs (NSAIDs) can be good alternative analgesics. In geriatric populations, NSAID use is not contraindicated as long as there is no sign of renal impairment, hypotension, or dehydration.

In conclusion, anesthetic protocols for geriatric compared with younger patients differ in how and when the drugs are administered, the detailed preoperative evaluation, the intensive intraoperative monitoring, and the extra effort involved in ensuring adequate postoperative analgesia.

ANALGESIA IN THE POLYTRAUMA PATIENT

Polytrauma, defined as significant traumatic injuries affecting more than one body region, is usually the result of high-energy impact (e.g., road traffic accidents, high-rise falls, and gunshot wounds). Worldwide, about 16,000 people each day die as a result of trauma (7). A survey showed that more than 13% of all patients were referred to veterinary hospitals for evaluation of trauma (8). Initial patient evaluation should be rapid and center on provision of life support. Evaluation of vital signs, including level of consciousness and adequacy of airway, breathing, and circulation, should be the first step of triage. The cardiovascular system should be monitored continuously once the patient is admitted to the hospital. Patients should have a large-bore catheter placed for vascular access. After initial assessment, further diagnostic tools should be used to rule out chest contusion, pneumothorax, traumatic myocarditis, intracavity hemorrhage, hypovolemia, and neurologic lesions. Adequate fluid resuscitation, inotropic drugs, and oxygen supplementation should be administered to improve oxygen delivery in a timely fashion.

Polytrauma patients are at a high risk for a severe systemic inflammatory response, leading to traumatic shock and consequent organ failure (9). An understanding of the systemic effects of severe trauma is therefore important to successfully assess and treat injured patients. In physiologic terms, trauma is a combination of severe tissue injury, hemorrhage, and pain. The systemic responses to these insults include involvement of the cardiovascular, neuroendocrine, metabolic, and immunologic systems (10).

The acute tissue injury caused by trauma triggers pain and activates the hypothalamic–pituitary–adrenal axis. The stress response that occurs after multiple traumatic injuries accounts for a high percentage of the mortality seen in trauma patients. In several studies, inadequately treated acute pain has been shown to increase this response, resulting in higher morbidity. Ensuring that animals are comfortable is therefore important from more than just a humane standpoint. It is becoming clear that providing appropriate and safe analgesia in polytrauma patients promotes a faster return to normal activity, shorter time in the hospital, better quality of life, and improved outcomes (10). Effective pain management in trauma patients requires an understanding of both the physiologic response to injury and the potential modification of the response produced by analgesic agents. Because pain is a major component of polytrauma and has many deleterious systemic effects, it is incumbent on the clinician to consider aggressive pain management as a core tenet of care in trauma (1). Pain control of the trauma patient should be an integral part of the overall care plan and can be divided into two main stages: the prehospital phase (patient restraint and temporary coaptation) and the hospital phase (assessment and analgesic treatment in the emergency department). Trauma-associated pain is complex and multifactorial that requires a thoughtful approach using a variety of treatment methods to achieve an optimal outcome. The goal is control of both nociception and neuroplasticity (10).

Analgesia of the trauma patient may be achieved either by administration of systemic analgesic agents via various routes or by neural blockade. The intravenous (IV) route is always advisable for systemic analgesia. Injection directly into the circulatory system allows immediate distribution of the analgesic to the nervous tissue. Drugs can be administered IV either as a bolus or preferably by continuous infusion, which can be titrated to effect to reduce the risk for rebound pain. Intramuscular and subcutaneous administration would lead to slower and unreliable systemic absorption, especially in patients that are hypovolemic and peripherally vasoconstricted.

Epidural analgesia is achieved by introducing analgesics into the epidural space. Injuries to the abdomen, pelvis, hindlimbs, and soft tissues of the posterior portion of the body may benefit from epidural analgesia. The most frequently used medications for epidural analgesia are local anesthetics, opioids, or combinations of these drugs (11). Alpha-2 agonists have also been used, either alone or in combination with local anesthetics or opioids. When combined with morphine they induce a longer-lasting analgesia than morphine alone (13 hours vs. 6 hours). However, practitioners should expect that systemic absorption of alpha-2 agonists from the epidural space may result in some undesirable effects. The most significant advantages of the epidural route in comparison to IV administration are the reduced dose of drug required, longer duration of analgesia, and superior analgesic effect. Unfortunately, epidural analgesia is contraindicated in patients with coagulation disorders, spinal injuries, or skin infections (11).

A multimodal (or balanced) approach to pain management takes advantage of the different modes and sites of action of various analgesic agents (12). Multimodal analgesia involves the use of two or more agents from different drug classes combined, to provide either an additive or synergistic effect. By doing this, the dose can potentially be lowered, thereby reducing the possibility of undesirable side effects. Another advantage is that the different mechanisms of action of the drugs provide more effective pain control at different levels. Protocols for balanced analgesia may range from administration of different classes of drugs in the same syringe, such as an alpha-2 agonist together with ketamine and an opioid, up to the combined use of locoregional anesthesia, an IV opioid bolus, and ketamine infusion (**Table 1**). Use of drugs that act at different sites within the central and peripheral nervous systems minimizes the dose of each single agent (12).

Table 1. Analgesia Drugs Classes and Comments

Drug Class	Effects and Side Effects	Use in Polytrauma
Alpha-2 agonist	Good analgesia, muscle relaxation, and sedation; side effects include bradycardia, vasoconstriction, and vomiting	Not recommended for hypovolemia or shock; avoid in polytrauma
Phenothiazine (acepromazine)	No analgesic properties but provides sedation and relaxation (stress enhances pain); side effects at high doses include vasodilatation and hypotension	Not recommended for hypovolemia, dehydration, or shock; avoid in polytrauma
Local anesthetic	Blocks nerve impulse and pain recognition; at appropriate doses, few systemic side effects	Local blockade is good; provides excellent analgesia with few systemic effects
NMDA-receptor antagonist (ketamine)	Reduces central sensitization and "wind-up"; good for chronic pain	Good adjunctive analgesic drug in polytrauma; use as an intravenous infusion
Steroids	Good anti-inflammatory and long-lasting; side effects include gastrointestinal bleeding, renal disease, immunosuppression, and risk for infection	Not recommended for hypovolemia, dehydration, or shock; avoid in polytrauma and do not use concomitantly with NSAIDs
NSAIDs	Good analgesia and anti-inflammatory; long-lasting; side effect include gastrointestinal bleeding, decrease platelet function, renal and hepatic disease	Not recommended for hypovolemia, dehydration, or shock; avoid in polytrauma and do not use concomitantly with steroids
Opioids	Good analgesic and sedation; side effects include bradycardia and histamine release (in some cases)	Good option for polytrauma patients; titrate to effect; a preferred analgesics for acute pain
Tramadol	Good analgesic, useful for chronic pain	Good analgesic option requires oral administration

NMDA = N-methyl-D-aspartate; NSAIDs = nonsteroidal anti-inflammatory drugs.

However, use of several drugs combined introduces a significant variable, which is the effect of one drug on the concentrations of the others at their sites of effect. This is usually unpredictable; it is therefore important to stress that the minimum number of drugs necessary to achieve optimal control of pain should be chosen. A possible initial approach to multimodal analgesia in traumatized patients may be to include an anxiolytic, an opioid, and a locoregional block. The choice of whether to include a sedative depends on the patient's temperament (13). Omission of a sedative may be desirable in calm patients. On the other hand, if there is potential for aggression, sedation may be required to ensure personnel safety and allow appropriate treatment.

In conclusion, several options exist to provide analgesia for the polytrauma patient. The ideal protocol will most likely include manipulation of the drug regimen, combination of different classes of analgesics, and some type of regional anesthesia technique.

ANESTHESIA FOR CATS WITH LOWER URINARY TRACT OBSTRUCTION

Patients with lower urinary tract obstruction are at risk for severe hyperkalemia; this condition should be considered an emergency. Clinical signs of severe hyperkalemia include lethargy, muscle tremors, and bradyarrhythmia. The main initial goal of therapy is to lower the serum potassium concentration and restore micturition (14). After relief of obstruction, hyperkalemia usually resolves within 24 hours, whereas azotemia and hyperphosphatemia require longer periods to resolve (15).

In cases of urinary obstruction, general anesthesia is often required for urinary catheter placement to allow retropulsion of the urethral calculi or to perform urethrostomy. Anesthesia for these patients is divided into three areas of concern: the disease process, electrolyte disturbances, and the anticipated consequences of the procedure. When planning to anesthetize a patient, it is important to systematically analyze all disease processes separately and to consider their possible interaction with the anesthetic agents. Urethral catheter placement is a relative benign procedure. Potential procedural problems include pain, urethral or bladder rupture, and increased vagal reflex from manipulation of the bladder.

Premedication

When the patient is lethargic, urinary catheterization can usually be performed with only sedation. The main concern is bradyarrhythmias due to hyperkalemia. With this in mind, drugs best avoided in urethral obstruction include xylazine, dexmedetomidine, and romifidine. An intravenous combination of buprenorphine and midazolam should produce mild sedation. Opioids cause minimal cardiovascular depression and should have a good margin of safety in these patients. In cases where the patient is not cooperative or attempts at urinary catheterization have been unsuccessful, general anesthesia should be elected to minimize stress (16, 17).

Induction

One of the main concerns during induction is avoidance of bradycardia, stress, and myocardial depression (16). With this in mind, ketamine with diazepam or tiletamine with zolazepam may be good short-acting induction agents. Induction agents should be given intravenously until the level of anesthesia permits endotracheal intubation. In cats, norketamine, an active metabolite of ketamine, is excreted unchanged by the kidneys, but prolonged recovery is unlikely unless urinary outflow cannot be reestablished. If this is the case, repeated doses of ketamine should be avoided (17).

Maintenance

Inhalant anesthetics are a good option for anesthesia maintenance. Hypoventilation can lead to respiratory acidosis. As with any type of acidosis, this will cause efflux of intracellular potassium in exchange for entry of extracellular hydrogen into the cell, which exacerbates hyperkalemia. Animals with mild hyperkalemia (6–7 mEq/L) can develop arrhythmias during general anesthesia even in the absence of earlier electrocardiographic abnormalities. Monitoring should include capnography, ECG, noninvasive blood pressure (Doppler), pulse-oximetry, and blood gas analysis. A good intraoperative maintenance fluid is 0.9% sodium chloride (15).

Agents for retrograde urethral flushing should be selected with care. Local anesthetics (i.e., lidocaine) are rapidly absorbed through damaged and hyperemic mucosa. Cats are particularly sensitive to lidocaine. Lidocaine is contraindicated in the face of slow idioventricular rhythms, escape beats, and bradycardia with absent P waves.

It is important to note that before general anesthesia and catheter placement, palliative therapy for hyperkalemia is recommended, especially if the patient is showing clinical signs of electrocardiographic abnormalities. Palliative therapy for hyperkalemia includes administration of potassium-free fluid (0.9% saline), calcium gluconate, dextrose, and sodium bicarbonate. Co-administration of insulin and sympathomimetic drugs can also help to decrease plasma levels of potassium. Administration of 0.9% saline helps to correct hypotension and hypovolemia and dilutes hyperkalemia. Calcium gluconate administration does not decrease serum potassium; however, it increases the extracellular fluid concentration of calcium and increases the threshold potential, thus restoring normal membrane excitability. Administration of sodium bicarbonate can alter the flux of potassium across the cell membrane. Sodium bicarbonate drives potassium into cells in exchange for hydrogen ions, which counteracts the increase in pH caused by the bicarbonate itself. Glucose administration increases endogenous insulin release and increases intracellular transport of potassium (14). Co-administration of insulin can prevent hyperglycemia and facilitate the movement of potassium. Other therapy methods include administration of beta-adrenergic agonists, such as albuterol, terbutaline, and epinephrine, which may be used to activate adenosine triphosphate–dependent potassium channels and therefore increase cellular influx of potassium (15).

Recovery and Postanesthetic Management

The patient should be recovered in a quiet area. It is advisable to monitor the patient for about 3 hours after general anesthesia because this is when anesthesia-related fatalities are most likely to occur (6). Urinary obstruction can be painful, and animals should be treated with analgesics and monitored overnight. Buprenorphine IV every 8–12 hours for 24 hours is an adequate choice (13). Due to possible renal damage, dehydration, and hypotension, NSAIDs are not recommended for these cases until normal blood volume and pressure are established and renal function is reevaluated.

Urine production after obstruction is usually greatly increased, which could cause dehydration along with significant electrolyte abnormalities. Following postobstruction diuresis, adequate fluid, and electrolyte administration must be provided to maintain renal function and hydration (18).

ANESTHESIA FOR CATS WITH HYPERTROPHIC CARDIOMYOPATHY

One of the most common cardiac diseases in cats, hypertrophic cardiomyopathy (HCM), is characterized by stiffness of the left ventricle with poor diastolic function. A recent epidemiologic study reported that 13% of healthy cats have HCM, although they do not have clinical signs and are normal on physical examination. It is speculated that a good percentage of anesthesia deaths in routine cases may be secondary to undiagnosed cardiac disease (19).

There is now widespread acceptance that the subaortic gradient and associated increase in left ventricular (LV) pressure obstruct outflow. Such obstruction can occur acutely and unexpectedly, and its presence has been correlated with increased risk for congestive heart failure, stroke death, and sudden death. Outflow obstruction is determined by a number of structural abnormalities, including small LV outflow tract area; septal bulge; and hyperdynamic LV ejection, which pulls the mitral valve toward the septum. Patients with outflow obstruction have a massive drop in cardiac output and blood pressure (20).Outflow obstruction can be provoked by conditions that increase myocardial contractility, such as stress and tachycardia; it can also be triggered by hypovolemia, hypotension, and dehydration.

Before the animal is anesthetized, it is important to ensure proper hydration. However, overly aggressive fluid therapy may have negative consequences by promoting heart failure and pulmonary edema. It is paramount that anesthesia of a cat with HCM be accomplished with minimal stress to the patient.

Patient with LV outflow tract obstruction benefit from protocols that reduce heart rate and contractility, decrease

sympathetic stimulation, and increase filling pressure and afterload. Drugs that mildly depress myocardial contractility and reduce oxygen demand while maintaining systemic vascular resistance are excellent in avoiding LV outflow obstruction.

Adverse perioperative outcomes are not uncommon in HCM patients (with or without LV outflow obstruction) undergoing general anesthesia. Reported events include congestive heart failure, supraventricular and ventricular arrhythmias, systemic hypotension, and sudden death. Veterinarians should be prepared to promptly treat the hemodynamic changes that HCM patients may experience during general anesthesia (21).

Premedication

The main concern during premedication is stress and a sudden burst of catecholamines. Administration of anticholinergics, such as atropine and glycopyrrolate, should be avoided because of the potential for tachycardia and increased myocardial work and oxygen demand. Other drugs that can cause iatrogenic LV outflow obstruction include inotropes and catecholamines, such as dobutamine, dopamine, and ephedrine. In this case, positive inotropes can produce a paradoxic effect (exacerbation of hypotension) (1).

HCM patients have increased myocardial mass with poor coronary perfusion and consequently are more prone to cardiac ischemia. For patients with no clinical signs of cardiomyopathy, a combination of opioids and midazolam is a safe choice, although this provides only mild sedation in cats. Midazolam or diazepam is indicated to blunt sympathetic activation. (22). These drugs have little cardiac depressive effect (13). For animals with a diagnosis of dynamic LV outflow obstruction, an IV combination of opioids and low-dose dexmedetomidine should yield effective sedation. Dexmedetomidine decreases catecholamine secretion and causes myocardial depression, bradycardia, and increased systemic vascular resistance (23). These are all desired effects in HCM with outflow obstruction (24).

Induction

One of the main concerns during induction is avoidance of severe vasodilatation, tachycardia, arrhythmias, stress, and myocardial ischemia. With this in mind, ketamine and diazepam or tiletamine with zolazepam are not good choices of induction agent. Etomidate causes almost no change in the hemodynamic state of the patient and little change in systemic vascular resistance. Induction agents should be given intravenously until the animal is sedated sufficiently to permit endotracheal intubation without any sign of stress (21).

Maintenance

Myocardial depression is usually desirable during anesthesia maintenance; therefore, volatile anesthetics are indicated in patients with HCM. Sevoflurane minimally reduces cardiac output and is associated with less vasodilation than isoflurane at typical anesthetic doses. Inhalants that can be arrhythmogenic (e.g., halothane) or can lead to catecholamine release (e.g., desflurane and nitrous oxide) should be avoided.

Hypoventilation should be corrected; however, a drop in venous return due to positive pressure ventilation is poorly tolerated and may cause acute outflow obstruction. Small tidal volumes and higher respiratory rates should be used if mechanical ventilation is required. Minimal monitoring should include capnography, ECG, noninvasive blood pressure (Doppler), and pulse-oximetry (25). HCM can lead to a variety of arrhythmias during anesthesia, and continuous monitoring of heart rate and rhythm is paramount before, during, and after surgery. Invasive blood pressure monitoring is also important to rapidly diagnose any decrease in blood pressure and pulse wave alternans (25). Treatment of hypotension may require volume replacement and administration of an alpha-1–agonist (phenylephrine). Dopamine and other beta-agonist drugs are poor choices because the increased inotropy and chronotropy associated with use may promote LV outflow obstruction. Vasodilators are also not indicated to treat hypertension because they decrease systemic vascular resistance and preload (21).

Recovery and Postanesthetic Management

Vigilance during the recovery period with respect to any increase in sympathetic response remains a priority. Stress,

pain, hypothermia, and hypovolemia can all lead to catecholamine release, resulting in increased myocardial oxygen demand and promoting dynamic outflow obstruction and malignant arrhythmias. Analgesics that can be titrated and are easily reversible should be provided; depending on the procedure, IV infusion of fentanyl for 24 hours may be an adequate choice. The patient should be recovered in a quiet area. Heart rhythm and blood pressure (if possible) should continue to be monitored for about 3 hours after general anesthesia because this is the high-risk period for anesthesia-related fatalities. Due to the possibility of hypotension, NSAIDs are not given immediately after surgery—they should not be administered until normal blood volume and pressure are established and renal function is reevaluated (1).

During the past decade, vast and sometimes contradictory literature has accumulated regarding HCM. During anesthesia, veterinarians should be aware of and recognize relevant pathophysiologic mechanisms that may trigger or accentuate dynamic LV outflow obstruction while also developing strategies to immediately respond to and effectively reverse this complications resulting from the interaction of anesthesia and HCM (24).

REFERENCES

1. Tranquilli WJ, Thurmon JC, Grimm KA, Lumb WV. Lumb & Jones' Veterinary Anesthesia and Analgesia. 4th ed. Ames, IA: Blackwell; 2007.
2. Carpenter RE, Pettifer GR, Tranquilli WJ. Anesthesia for geriatric patients. Vet Clin North Am Small Anim Pract. 2005;35:571-580.
3. Joubert KE. Pre-anaesthetic screening of geriatric dogs. J S Afr Vet Assoc. 2007;78:31-35.
4. Paddleford RR. Anesthetic considerations for the geriatric patient. Vet Clin North Am Small Anim Pract. 1989;19:13-31.
5. Evans T. Anesthesia for the geriatric patient. Vet Clin North Am Small Anim Pract. 1981;11:653-667.
6. Brodbelt DC, Blissitt KJ, Hammond RA, et al. The risk of death: the confidential enquiry into perioperative small animal fatalities. Vet Anaesth Analg. 2008;35:365-373.
7. Davenport RA, Tai N, West A. A major trauma centre is a specialty hospital not a hospital of specialties. Br J Surg. 2010;97:109-117.
8. Kolata RJ. Trauma in dogs and cats:an overview. Vet Clin North Am Small Anim Pract. 1980;10:515-522.
9. Kroupa J. [Definition of "polytrauma" and "polytraumatism"]. Acta chirurgiae orthopaedicae et traumatologiae Cechoslovaca. 1990;57:347-360.
10. Keel M, Trentz O. Pathophysiology of polytrauma. Injury. 2005;36:691-709.
11. Branson KR, Ko JC, Tranquilli WJ, et al. Duration of analgesia induced by epidurally administered morphine and medetomidine in dogs. J Vet Pharmacol Ther. 1993;16:369-372.
12. White PF. Multimodal analgesia: its role in preventing postoperative pain. Curr Opin Invest Drugs. 2008;9:76-82.
13. Robertson SA. Managing pain in felinie patients. Vet Clin North Am Small Anim Pract. 2008;38:1267-1290, vi.
14. Rieser TM. Urinary tract emergencies. Vet Clin North Am Small Anim Pract. 2005;35:359-373, vi.
15. DiBartola SP. Management of hypokalaemia and hyperkalaemia. J Feline Med Surg. 2001;3:181-183.
16. Raffe MR, Caywood DD. Use of anesthetic agents in cats with obstructive uropathy. Vet Clin North Am Small Anim Pract. 1984;14:691-702.

17. Robertson S. Anesthesia for feline urethral obstruction. Vet Clin North Am Small Anim Pract. 1992;22:475-478.

18. Dibartola SP. Fluid, Electrolyte and Acid-Base Disorders in Small Animal Practice. 3rd ed. Philadelphia,: Elsevier Saunders; 2006.

19. Paige CF, Abbott JA, Elvinger F, Pyle RL. Prevalence of cardiomyopathy in apparently healthy cats. J Am Vet Med Assoc. 2009;234:1398-1403.

20. Poliac LC, Barron ME, Maron BJ. Hypertrophic cardiomyopathy. Anesthesiology. 2006;104:183-192.

21. Bednarski RM. Anesthetic concerns for patients with cardiomyopathy. Vet Clin North Am Small Anim Pract. 1992;22:460-465.

22. Akkerdaas LC, Mioch P, Sap R, Hellebrekers LJ. Cardiopulmonary effects of three different anaesthesia protocols in cats. Vet Q. 2001;23:182-186.

23. Lamont LA, Bulmer BJ, Sisson DD, et al. Doppler echocardiographic effects of medetomidine on dynamic left ventricular outflow tract obstruction in cats. JAVMA. 2002;221:1276-1281.

24. Baty CJ. Feline hypertrophic cardiomyopathy: an update. Vet Clin North Am Small Anim Pract. 2004;34:1227-1234.

25. Haskins SC. Monitoring the anesthetized patient. In: Tranquilli WJ, Benson LN, eds. Lumb and Jones's Veterinary Anesthesia and Analgesia. Ames, IA: Blackwell; 1996:409-425.