

PERSPECTIVES

by Rhonda Hovan

Preventive Health Care Thru Risk Management

Dog breeders are accustomed to thinking about preventive health care beginning with the selection of sire and dam. Hip, elbow, eye, and heart clearances are usually high on the list of prerequisites. In addition, many breeders try – to the best of their ability – to consider factors such as skin and allergy problems, epilepsy, cancers, hypothyroidism, and other common health issues in the breed. It is a daunting and frequently frustrating task.

Of course, such genetic selection is not practiced in human reproduction, except under very specialized circumstances. Preventive health care usually bypasses the selection of parents (genes), and is focused instead on identification and management of risk factors. And without any organized effort to modify the human gene pool (as is the case with dog breeding), risk management has proven to be an amazingly effective method for extending both quality of life, and longevity. While the field of risk management is far better researched for humans, there is compelling and increasing evidence that similar preventive management strategies may also benefit dogs. In some circumstances, risk management may, in fact, impact canine health and longevity to a similar or even greater degree than genetic selection.

An Ounce of Prevention

In 1987, researchers at Purina began a landmark study of 48 age and sex matched Labrador Retrievers (24 pairs) (1). Beginning at eight weeks of age, one member of each pair was permitted to eat all it wanted; while its pair-mate was fed 75 percent of that amount. After the age of 3.25 years, the free-fed member's food was restricted to prevent obesity; and the pair-mate received 75 percent of that restricted amount. The dogs were monitored throughout their lives for numerous indicators of health and aging.

Results were dramatic, with the food-restricted dogs showing a median life span that was 22 months longer than the free-fed group. In addition, the food-restricted dogs had a lower rate and older age of onset of cancer, osteoarthritis, and liver disease than did their pair-mates. Restricted food studies have shown similar results in a variety of other animals including mice and rats, and preliminary results in rhesus monkeys. There are no breeding selection factors that are known to have as great an impact on overall longevity as this study indicated is possible with calorie restriction.

Examination of the data in greater detail² shows a five times greater prevalence of osteoarthritic lesions in the hip

joints of free-fed dogs versus food-restricted dogs. And while the number of lesions in the elbow joint was not significantly higher among free-fed dogs, the severity of the elbow disease was increased in the free-fed dogs. A further finding was a significantly higher rate of false pregnancies among the free-fed bitches, as compared to the food-restricted group.³

Birth to Eight Weeks

The above data compares the results of dogs with differing calorie intake beginning at eight weeks of age. Although canine "birth to death" feeding studies have not yet been done, there is some indication that the period from birth to eight weeks may also play an important role in risk management. Studies of puppies that were bottle fed to produce a reduced rate of growth showed a lower incidence of hip dysplasia as compared to faster growing puppies⁴. Numerous studies have confirmed that while hip dysplasia is not present at birth, changes associated with HD begin within the first several weeks of life.⁵ Even in the absence of additional data, current information suggests that a prudent course of risk management might be to monitor and control the calorie intake of litter age puppies to produce a reduced rate of growth.¹

¹ A guideline that this author uses is to permit a rate of growth from birth to seven weeks that does not exceed the puppy's age in weeks + one pound (e.g., a three-week-old puppy should weigh four pounds; a six-week-old puppy should weigh seven pounds). However, by seven weeks the weight gain does begin to exceed one pound per week, and the eight week old goal weight is 9-10 pounds; while the 10 week old goal weight is 12 pounds; and the 16 week goal weight is 22-23 pounds.

Hints of another potential risk management strategy pertaining to litter age puppies come from decades of research in humans. It has been widely substantiated that human infants nursed only on breast milk until an older age have significantly reduced risk of allergy and asthma throughout their lives, as compared with infants introduced to formula or solid food at a younger age.⁶ There is no comparable published research in dogs, and the value of extrapolating this human data to puppies is not known. However, in most circumstances, the decision of when to introduce formula or solid food to a litter is based on individual habits and practices rather than specific requirements of the situation. Such decisions can be easily modified. In a breed such as Golden Retrievers, where the lifetime risk for developing atopy is high (24.5 percent according to the 1998 Health Survey), a decision to postpone introduction of all non-bitch milk foods until a later date might be a proactive step toward mitigating this risk. ("Non-bitch milk" refers to any food that does not come from the dam, including bitch milk replacement formulas, and of course, all solid foods.) Most litters can be fed entirely by the dam until approximately five weeks of age.

Dietary Supplements

Numerous studies on humans over the past decade have suggested that dietary supplementation of antioxidants may have health benefits. Examples of antioxidants include beta-carotene, lycopene, and vitamins A, C, and E. Selenium is a mineral, not an antioxidant, but it is a component of antioxidant enzymes and is often grouped with antioxidants. A large, randomized human trial published in 1993 showed that a combination of beta-carotene, vitamin E, and selenium significantly reduced the incidence of a certain specific cancer and cancer overall,⁷ and subsequent research has frequently supported these findings. However, there are also some conflicting studies that did not find such benefits, and the position of the United States Preventive Services Task Force is that the evidence is currently insufficient to recommend for or against the routine use of antioxidant supplements in humans.⁸

Canine researchers have also begun to investigate antioxidant supplementation in dogs, and a recent study⁹ indicates the potential for some benefits: "These findings in dogs suggest that antioxidant

supplementation can achieve sustained increases in circulating levels of antioxidants that exert a protective effect by a decrease in DNA damage, leading to improved immunological performance. These findings also have implications in a wider context where free-radical damage has been associated with a variety of degenerative disorders and the aging process in general." Another study¹⁰ investigated the effect of supplementation with lutein (a carotenoid) on the immune system and concluded, "dietary lutein stimulated both cell-mediated and humoral immune responses in the domestic canine." Following the lead of similar studies in humans, a recent study of selenium supplementation in dogs¹¹ noted that: "These data suggest that dietary selenium supplementation decreases DNA damage and increases epithelial cell apoptosis within the aging canine prostate." However, all of the canine studies noted above examined the effects of antioxidant supplementation at the cellular level. As with humans, the research is promising but inconclusive and sometimes conflicting, and few studies examining the actual rate or age of onset of disease in supplemented dogs have been published. Nonetheless, the potential benefits are great enough and potential harm is minimal (providing that owners use care not to overdose, particularly with vitamin A), that concerned owners and breeders may want to consider a moderate level of dietary supplementation with antioxidants and selenium as a strategy to help manage multiple risks in Golden Retrievers, including immune system dysfunction, cancers, and age related changes.

Also of interest are the numerous studies in humans indicating the potential beneficial effects of dietary supplementation with cruciferous vegetables such as broccoli, cauliflower, Brussels sprouts, and cabbage. One very recent abstract¹² stated, "The American Institute of Cancer Research estimates that if the only dietary change made was to increase the daily intake of fruits and vegetables to 5 servings per day, cancer rates could decline by as much as 20%. Epidemiological studies provide evidence that the consumption of cruciferous vegetables protects against cancer more effectively than the total intake of fruits and vegetables." Another¹³ noted, "Cruciferous vegetables such as broccoli and cauliflower seem to be especially protective against cancer." Little similar

research has been conducted in dogs. However, one small study¹⁴ of Scottish Terriers genetically susceptible to transitional cell carcinoma (cancer of the urinary tract) appeared to find a protective association for dogs fed broccoli and cabbage three times a week. As with antioxidant supplements, the potential benefits of cruciferous vegetables have yet to be thoroughly investigated in dogs. However, given the high incidence of cancers in the breed, some owners may wish to consider moderate supplementation with cruciferous vegetables as a proactive strategy to possibly decrease the risk of cancer. As with other human foods (notably chocolate and caffeine), some vegetables (such as onions) and fruits (such as grapes and raisins) can be toxic to dogs even in small amounts. Owners should consult their veterinarian prior to adding novel foods to their dog's diet.

There are a few studies indicating potential disease prevention effects of a diet balanced with a specific ratio of omega-3 (n-3; found in fish oil) and omega-6 (n-6; or linoleic acid, found in vegetable oils) fatty acids. One noted, "In summary, this study indicates that feeding a diet containing an (n-6):(n-3) fatty acid ratio of 5:1 had a positive, rather than a negative, effect on the immune response of young or geriatric dogs."¹⁵ Although challenging because it is dependent on the ratio of these fatty acids in the dog's basic food, some owners might want to consider dietary supplementation with fatty acids to achieve the 5:1 (n-6):(n-3) ratio suggested in this study.

Less well investigated are the potential disease prevention effects, if any, of dietary supplementation with glucosamine hydrochloride and chondroitin sulfate (Cosquin[®]). While research¹⁶ in puppies has indicated that intramuscular injections of a product similar to glucosamine hydrochloride, called glycosaminoglycan polysulfates (Adequan[®]), appears to reduce the incidence of hip dysplasia, studies have not supported similar preventative effects of dietary supplementation with glucosamine (with or without chondroitin). However, supplementation with oral glucosamine hydrochloride and chondroitin sulfate has been demonstrated to be beneficial in the treatment of already existing osteoarthritis.

More Than a Pretty Smile

Probably most owners are aware that they "should" practice preventive dental care by brushing their dog's teeth. Owners know that brushing a dog's teeth can help prevent tooth decay and gum disease – this is nothing new. Still, most owners appear to neglect this aspect of daily care for their dogs, probably because they consider it to be low on the priority list of potential serious health concerns. However, there is emerging evidence in humans that periodontal disease may also have damaging effects throughout the body, and this is currently the topic of much scientific investigation. One recent study¹⁷ concluded, "Cumulative evidence suggests that periodontal disease can be an important cause of morbidity and mortality of various systemic diseases," and further detailed, "Examples of systemic infections that may involve oral microorganisms include infective endocarditis, aspiration pneumonia, <snip> and various other life-threatening infections. Inflamed gingiva constitutes a significant reservoir for herpes viruses." Another study¹⁸ confirmed, "A growing body of scientific evidence has shown that severe periodontitis may enhance susceptibility to certain important systemic diseases and conditions, for example, cardiovascular disease, diabetes mellitus, adverse pregnancy outcomes, and pulmonary infections."

These potential systemic effects of periodontal disease are less researched in dogs. Nonetheless, it is known that preventive dental care is widely neglected among dog owners, leaving much room for improvement. The impact of lack of regular brushing was noted in a study¹⁹ that concluded, "Periodontal disease is the most common disease affecting adult dogs and cats. It is also a very preventable disease. The insidious nature of the disease and requirement for the pet owner to be actively involved make client and public education absolutely vital. <snip> When successful, clients' pets will live healthier and longer lives."

As with humans, brushing is most effective when done daily.² Even regular periodic professional dental cleanings do not offer the potential benefits of brushing on a daily or near daily basis.²⁰ The welcome news for owners is that some of the commercially available canine dental hygiene chews do appear to offer ben-

efit in managing periodontal disease,²⁰ and may be a time-saving aid to home dental care. In addition, there are relatively new commercial foods that are specially formulated and processed to reduce dental disease. One study²² indicates that, "Daily feeding of the dental food significantly reduced plaque and gingivitis by 39% and 36%, respectively, compared with daily feeding of the typical dry food." However, dental chews, dental foods, and home scrapings are not a substitute for brushing at least every other day, because only brushing acts to reduce anaerobic bacteria that accumulate below the gum line.

1998 GRCA/GRF Health Survey

The 1998 GRCA/GRF Health Survey²³ provides some intriguing and useful data that may help owners make good decisions in several other areas of preventive health care. The report notes, "A significant decrease in the frequency of lymphosarcoma was found for Goldens whose owners reported exposure to flea/tick drops, shampoos, and sprays. Similarly, a significant decrease in hemangiosarcoma was found in association with use of flea/tick drops." The reasons for this inverse association are not known, but the Golden Retriever Foundation is currently funding investigation of one promising theory. This study will examine the possibility of an association between vector borne (transmitted via flea/tick bites) diseases such as *Ehrlichia* and/or *Bartonella* spp, and the subsequent development of lymphoma in Goldens. However, even while the underlying mechanisms responsible for the decreased rate of lymphoma and hemangiosarcoma in association with increased use of flea/tick products remain unknown, this survey result may still provide reassurance to owners that the overall effect of using these products to prevent or minimize external parasite infestation may be beneficial to their dogs.

Data related to the age at neutering may also provide owners with further information on which to base age-at-neutering decisions. The Health Survey reported that, "Both bitches and dogs neutered at less than 1 year of age were significantly taller as adults than those neutered at greater than or equal to 1 year of age, or intact animals." This relationship of adult height to age at neuter-

ing takes on greater significance when considered in light of the additional finding that, "Among bitches and dogs, the taller the animal as an adult, the shorter the lifespan. There was a difference of 1.1 and 2.2 years in the mean age at death between the tallest and the shortest bitches and dogs, respectively." In addition, neutered dogs and bitches showed an increased risk of hypothyroidism as compared to intact dogs and bitches, with an increase of approximately 80 percent and 60 percent, respectively, by sex.

In Summary

Risk management is a powerful yet often overlooked tool for improving the health and longevity of dogs. A dog's lifetime risk of developing disease is not merely the sum of all its genes, and good management can greatly reduce the likelihood that genotypic potential for disease will become phenotypic expression of disease. While not every owner will choose to incorporate every strategy, it is hoped that owners will consider implementing some of the strategies that may have the most potential benefits in the individual situation.

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² See the March-April 2004 *GRNews*, p 78-9, for a fuller discussion of canine dental care.

Perspectives, continued

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⁴ A study of 16 litters conceived from frozen semen showed that of 87 total puppies, 54% were conceived on Day 7 and 46% on Day 5. (Tsumagari S, et al)

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CHF Grant # 2629: Clinical and Immunological Outcomes in Dogs with Osteosarcoma Treated with Intratumoral Interleukin-12 Microspheres

Principal Investigator:
Stuart Helfand, DVM
University of Wisconsin

Abstract: Appendicular osteosarcoma, or bone cancer of the limbs, is an important tumor in dogs representing nearly 10% of all canine cancers. Despite progress in treating canine osteosarcoma using a combination of limb amputation and chemotherapy, life expectancy is not usually extended by more than 6-10 months compared to amputation alone. Death is due to dissemination of cancer cells beyond the leg and it is estimated that the cancer has already spread in at least 95% of dogs when it is initially diagnosed. Any pet owner who has lived through this disease can attest to the heartbreak of the news that tumor masses, initially undetectable at the time of diagnosis, have been discovered on a chest X-ray. Novel treatment regimens are urgently needed to improve the lives of large breed dogs such as Golden, Labrador and other Retrievers, Rottweilers, Irish Wolfhounds, Great Danes, German Shepherds and others that are at greatest risk for developing this cancer. Stimulating the immune system of dogs with cancer has been a goal of veterinary cancer researchers for more than 20 years and osteosarcoma is a tumor that has shown positive responses to some of these interventions. This research proposes to add a potent new form of immunostimulation to the standard treatment for canine osteosarcoma. This strategy uses a powerful stimulant of the immune system called interleukin-12 (IL-12) that has been shown to induce strong anti-tumor responses in experimental animal models. Stimulated by IL-12, immune cells tolerant of cancer can be triggered to kill cancer cells throughout the body, resulting in the generation of an army of deadly circulating killer immune cells specific for the cancer. What's more, this type of cell has long-term memory for the cancer, in much the same way vaccination results in long-term immunity to infectious disease. Our laboratory has shown that IL-12 enhances killing of osteosarcoma cells by immune cells from dogs with this cancer. Now, we propose that

injection of IL-12 directly into limb osteosarcoma using a novel (microsphere) formulation resulting in slow IL-12 release within the tumor environment will promote active antitumor immunity in dogs with osteosarcoma and lengthen their survival time. A number of pertinent immunological questions will also be addressed.

Start date and duration:
January, 2004 for 2 yrs.

Total funds approved by CHF:
\$151,909 over 2 yrs.

GRF contribution: \$6000 over 2 yrs.

Status: New, no report available

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*** CHF Grant # 2646: Characterization of Receptor Tyrosine Kinase Dysfunction in Malignant Histiocytosis**

Principal Investigator:
Cheryl London, DVM, PhD
University of California, Davis

Abstract: Malignant histiocytosis (MH), while rare in people, occurs frequently in certain breeds of dogs including Rottweilers, Golden Retrievers, Flat-Coated Retrievers and Bernese Mountain Dogs. There is no effective therapy for this disease and nearly all patients die within 2-4 months of diagnosis. The purpose of this proposal is to evaluate MH tumor specimens for mutations in genes that may contribute to the development of this devastating cancer. The genes of interest are those that code for proteins known as growth factor receptors. These proteins are present on the surface of the cell and when stimulated by growth factors, signal into the cell promoting cell survival and growth. Dysregulation of growth factor receptors is a common mechanism through which normal cells undergo transformation into cancer cells. Significant research has been directed towards the development of inhibitors capable of blocking the function of dysregulated receptors. Recent success of this approach has been realized with the inhibitor Gleevec in the treatment of chronic myelogenous leukemia in people. The purpose of this proposal is to identify growth factor receptors that are dysregulated in MH to provide the foundation for future clinical application of growth factor receptor inhibitors in the treatment of MH.

Start date and duration:
October, 2003 for 2 yrs.

Total funds approved by CHF:
\$96,517 over 2 yrs.

GRF contribution: \$10,000 over 2 yrs.

Status: Actively recruiting dogs with malignant histiocytosis.

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CHF Grant # 2657: Role of Circulating Endothelial Cells in Physiologic and Pathologic Angiogenesis in Dogs

Principal Investigator:
Steven Dow, DVM, PhD
Colorado State University

Abstract: Formation of new blood vessels (angiogenesis) is crucial to a number of important processes, including healing wounds, resolving inflammation, and stimulating the growth of tumors. Recent studies indicate that many of the new cells that are used to form new blood vessels actually come from the bloodstream. This observation raises several important questions, including how different disease states may affect that numbers of these cells in circulation and how the numbers of these circulating endothelial cells may be regulated. We propose to evaluate new assays to measure the numbers these circulating endothelial cells in the bloodstream of dogs, using small blood samples. These assays will be used to measure the numbers of these endothelial cells in the bloodstream of dogs with conditions that may affect formation of new blood vessels, including surgery, tumors, and clotting disorders. Circulating endothelial cells will also be grown in tissue culture and characterized. These studies will provide important new information on the role of the bone marrow and circulating endothelial cells in blood vessel formation in dogs and may help in the development of new strategies to either inhibit or stimulate blood vessel formation in different diseases.

Start date and duration:
January, 2004 for 2 yrs.

Total funds approved by CHF:
\$35,046 over 2 yrs.

GRF contribution:
\$2000 over 2 yrs. ❖