

# Current Perspectives in Senior Dog and Cat Nutrition



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# Summary of Contents

## CHAPTER 1: CANCER IN THE ELDERLY DOG

David J. Waters and Dawn M. Cooley

Pages 12-16

### Summary.

The treatment of cancer in elderly dogs presents unique challenges. The ability to treat the patient's tumor on the basis of its molecular signature will likely lead to improved prognosis for elderly dogs with cancer. Although cancer preferentially affects the elderly, meaningful progress in the reduction of cancer incidence will likely rely upon prevention strategies targeted to young adults at high risk for cancer development.

### Findings.

- Aging influences
  - The risk of cancer
  - The biological behavior of resultant cancers
  - Host:tumor cell interactions regulate virtually every aspect of tumor cell behavior
    - growth
    - metastasis
    - sensitivity to chemotherapeutic agents
  - Aging-related changes in homeostasis within host tissues may significantly impact the risk for development of lethal cancers
    - An old host provides an environment that is in some way better-suited for the survival and proliferation of tumor cells
    - Risk for most adult-onset cancers increases dramatically with increasing age
    - Host age may influence the biological behavior of malignant tumors
      - ▲ In dogs with prostate carcinoma, young dogs had a significantly greater likelihood of skeletal metastases at time of cancer diagnosis than older dogs
      - ▲ For young dogs < 6 months of age, the three most common tumor sites were hematopoietic system, brain, and skin
      - ▲ Vascular tumors of young dogs were 4X more likely to be benign than vascular tumors that developed in elderly dogs
  - Age-specific cancer mortality rate begins to decline in very old dogs
    - Cancer resistance genes are overrepresented in the oldest-old, where they may influence longevity by protecting the host from malignant disease
- Optimizing the treatment of cancer in the elderly patient
  - Nutrition may play an important role
  - Treatment based upon molecular signature of the patient's tumor, rather than on tumor type
  - Elderly dogs may not be most appropriate targets for cancer prevention interventions
    - Direct cancer prevention strategies toward young adults rather than the elderly
    - Ovariohysterectomy has a protective effect on the subsequent development of mammary cancer in dogs
    - Diet and body conformation early in life may also influence mammary cancer risk

## CHAPTER 2: NUTRITIONALLY MANAGING GLUCOSE METABOLISM IN THE SENIOR DOG AND CAT

Gregory D. Sunvold and Michael G. Hayek

Pages 17-21

**Summary.** Research shows that aging alters glucose metabolism. Recent nutritional concepts that promote improved glucose metabolism include: 1) sorghum and barley as carbohydrate sources; 2) a viscous fiber, carboxymethylcellulose (CMC); 3) a fermentable fiber blend; 4) chromium tripicolinate; and 5) carnitine. By utilizing diets that incorporate these concepts, one can help meet the goal of improving glucose metabolism in senior animals. Maintaining normal glucose metabolism as the individual ages may help avoid disease and thus may promote longevity.

**Findings.**

- Changes in glucose metabolism observed with age
  - Senior dogs have delayed glucose absorption, compared with young dogs
  - Insulin sensitivity is reduced in senior dogs
  - Older cats had lower glucose effectiveness, compared with younger cats
- The primary nutritional concept that has been implicated for improving glucose metabolism is the use of high-fiber diets. However, these diets can have a number of adverse effects and may not result in weight loss
- Results from studies in both dogs and cats suggest that dietary starch source is important in older animals, since their glucose metabolism is generally impaired compared with younger animals
- Use of a viscous fiber source may blunt the rise in blood glucose immediately following a meal
  - Carboxymethylcellulose (CMC) consists of cellulose modified to enhance its viscosity
  - When 1% high-viscosity CMC was added to the diet, postprandial blood glucose decreased
- Chronic feeding to dogs of a diet containing a fermentable fiber blend increased insulin levels after an oral glucose load
  - Resulting in a blunted rise in blood glucose levels
- Supplementation with chromium tripicolinate
  - Improved the ability of dogs to clear glucose from their blood
  - Increased insulin sensitivity in dogs
  - Improved glucose metabolism in cats in a dose-dependent manner
  - Aided in preserving lean body mass in cats, at the expense of body fat
    - Reduced fat mass is associated with improved insulin sensitivity
- Carnitine supplementation in weight loss diets of dogs and cats promotes fat metabolism, which may indirectly improve glucose metabolism status

**Application.** Eukanuba Veterinary Diets® Nutritional Weight Loss Formula™ Restricted-Calorie™, Nutritional Weight Maintenance Formula™ Glucose-Control™ and Nutritional Joint Maintenance Formula™ Senior Plus contain nutrients that enhance glucose tolerance and insulin sensitivity. The use of these nutrients in the diet may help maintain normal glucose metabolism as the dog or cat ages.

## CHAPTER 3: NUTRITION AND AGING IN COMPANION ANIMALS

Michael G. Hayek, Gary M. Davenport, and Michael A. Ceddia

Pages 22-27

**Summary.** Aging changes the metabolism and physiology of dogs and cats, which may result in differences in the way geriatric animals utilize nutrients and their overall nutrient requirements. Therefore, specific nutritional formulations are warranted for the aging population companion animals. Strategies should be designed to prevent the onset of age-associated physiological changes (ie, decline in lean body mass and immune response) as well as adjust to progressive metabolic changes (ie, changes in enzyme activities for fatty acid metabolism).

**Findings.**

- Older dogs and cats have a decreased ability to regulate blood glucose
- The activity of some enzymes involved in fatty acid metabolism may be altered with age
- Aging alters regulation of the immune system and may increase susceptibility to disease in geriatric animals
  - The rate of age-related decline may be different between breeds of dogs
  - In one study, both Fox Terriers and Labrador Retrievers demonstrated an age-associated decline in their ability to respond to the different mitogens, but the responses of the Fox Terriers declined more than the Labradors
  - Antioxidants such as vitamin E,  $\beta$ -carotene or lutein have been shown to have beneficial effects on the canine and feline immune system
- Skeletal muscle is highly vulnerable to the effects of aging
  - During aging, loss of body protein results when protein degradation exceeds synthesis
  - Alterations in whole-body protein turnover are ultimately responsible for muscle wasting
    - Muscle protein turnover accounts for 30% of the whole-body protein turnover in young-adults, but decreases to 20% as individuals age
    - Rates of whole-body protein synthesis and degradation were 2-fold higher when dogs consumed a diet containing 32% protein compared with those consuming diets containing 16 and 24% protein
  - Loss of lean body tissue may diminish the body's ability to respond to physical trauma or infectious agents or stress

**Application.** Current research in dogs and cats supports the concept that geriatric animals have unique nutritional requirements and should be fed accordingly. Eukanuba Veterinary Diets® Senior Plus, Eukanuba® Senior Formula, and Iams® Active Maturity™ Formula take into account moderate protein levels, antioxidant vitamin adjustments, and specific fatty acids in order to address these issues.

## CHAPTER 4: BALANCED NON-SURGICAL MANAGEMENT OF OSTEOARTHRITIS IN THE OLDER DOG

Steven A. Martinez

Pages 28-33

**Summary.** Osteoarthritis can be a debilitating disease for geriatric dogs; however, new concepts in a balanced management of OA can result in an acceptable quality of life for the OA patient. No single treatment will adequately manage osteoarthritis (OA) in all dogs. A combination of three treatment components should be considered when medically managing a dog with OA: 1) weight control, 2) exercise/activity, and 3) pharmacological/disease-modifying osteoarthritic drugs. Exclusion of one or more of these components from a treatment protocol will usually result in an overall poorer clinical response.

**Findings.**

### **Weight Control**

- Obesity is a major risk factor for the development of OA
- Overweight dogs that achieved an 11–18% body weight reduction were significantly less lame compared with their pre-weight loss lameness scores
- Dogs with OA that inhibits movement cannot utilize consumed or stored fat efficiently
- Dogs with underlying endocrine disorders have a tendency to maintain body fat even when fed a reducing diet

### **Exercise**

- Controlled exercise is an important aspect in the management of OA in dogs
- High-impact activities may over-stress damaged joints and increase inflammation
- Low-impact activities are thought to reduce loads on affected joints and result in less discomfort for the patient while maintaining good muscle strength/mass and joint function

### **Pharmacologics**

- The primary goal of the pharmacological management of OA is to relieve the patient of discomfort associated with joint movement
- Toxicity concerns are present with long-term, chronic therapy with non-steroidal anti-inflammatory drugs; therefore, they probably should be administered only on an as needed basis, especially for the dog that has only intermittent discomfort due to OA
- Glucosamine and chondroitin sulfate reportedly have a positive effect on the cartilage matrix; they enhance proteoglycan production and inhibit catabolic enzyme production or activity in arthritic joints

**Application.**

Diets such as Eukanuba Veterinary Diets® Nutritional Joint Maintenance Formulas™ Senior Plus/Canine that help maintain healthy body weight and contain ingredients that may help maintain joint health can play an important part in managing dogs with OA.

## CHAPTER 5: EARLY DETECTION AND MANAGEMENT OF CANINE RENAL DISEASE

Gregory F. Grauer

Pages 34-37

**Summary.** Renal disease leading to chronic renal failure (CRF) is a major cause of morbidity and mortality in dogs. Early detection of canine renal disease, prior to the onset of CRF, should improve our ability to manage these patients. Proteinuria can indicate the presence of glomerular disease prior to the onset of azotemia. Although a direct pathogenetic link between glomerular disease, proteinuria, and progressive renal damage has not been established in the dog, attenuation of proteinuria has been associated with attenuation of renal functional decline in several canine studies.

**Findings.**

- Chronic renal failure (CRF)
  - The cause of CRF is usually difficult to determine
  - Most canine CRF occurs in middle to older aged dogs
  - Clinical signs of CRF are nonspecific and include lethargy, anorexia, vomiting, dehydration, and emaciation. A diagnosis of renal failure is confirmed when persistent azotemia with concurrent isosthenuria or minimally concentrated urine is documented
  - Increases in serum urea nitrogen, creatinine, and phosphorus, or urinary excretion of protein may signal the onset of renal disease
  - Dogs may also become more susceptible to bacterial urinary tract infections as their ability to concentrate urine decreases and the antibacterial properties of their urine decreases
- Canine glomerular disease
  - Is relatively common and can lead to chronic renal insufficiency/failure
  - Proteinuria can cause glomerular and tubular damage and result in progressive nephron loss
    - Proteinuria can occur secondary to immune-mediated glomerular damage or as a consequence of the nephron hypertrophy and glomerular hyperfiltration that results from nephron loss
  - Most canine glomerular disease is thought to be associated with the presence of immune complexes in glomerular capillary walls
- Evidence linking proteinuria to progression of renal disease in dogs is not entirely convincing
  - There does not appear to be a relationship between proteinuria and glomerular filtration rate in dogs with glomerulonephritis
  - Angiotensin converting enzyme inhibition and omega-3 fatty acid supplementation have decreased proteinuria and slowed progression
  - Calcium blockade treatment resulted in increased mesangial cell proliferation despite decreasing proteinuria
  - Reduction of dietary phosphorus decreased renal disease progression in remnant kidney dogs but had no effect on proteinuria
- Supportive therapy is important in the management of proteinuric renal disease
  - Sodium-reduced diets (<0.3% dry matter)
  - Vasodilators and diuretics used as necessary
  - Reduction of systemic hypertension may reduce intraglomerular hypertension
  - Reduced-quantity, high-quality protein diets should also be recommended in an attempt to decrease glomerular hyperfiltration and proteinuria

## CHAPTER 6: VITAMIN E, IMMUNITY, AND AGING

Simin Nikbin Meydani, Michael A. Ceddia, and Michael G. Hayek

Pages 38-43

- Summary.** Vitamin E is one of the most powerful biological antioxidants; its main function is to protect cellular lipids against oxidation. An optimal level of vitamin E is needed in all age groups for maintenance of the immune response. This need, however, seems to be more critical in aged animals. Given the fact that enzymatic antioxidant defenses are reduced in aging and that high levels of some antioxidants are reduced in the elderly, the aged immune system could potentially benefit from increased intake of vitamin E. Vitamin E supplementation appears to enhance immune response and may protect animals against infections and/or disease.
- Findings.**
- Splenocytes from old mice fed 500 ppm of dietary vitamin E had a significantly higher proliferative response to Con A and lipopolysaccharide than did control animals fed 30 ppm of vitamin E
    - Vitamin E supplementation significantly increased DTH to 2,4-dinitro-7-fluorobenzene
    - This immunostimulatory effect of vitamin E was associated with increased production of IL-2 and decreased production of PGE<sub>2</sub>
  - Vitamin E supplementation was associated with increases in plasma vitamin E, DTH score, and mitogenic response to Con A and IL-2 production in human subjects
    - Vitamin E supplementation was associated with decreases in PHA-stimulated PGE<sub>2</sub> production by peripheral blood mononuclear cells (PBMC) and plasma lipid peroxide levels
    - No effect on the mitogenic response of PBMC to PHA or IL-1 production was observed
  - A significant reduction was observed in lung influenza viral titers of mice supplemented with 500 ppm of vitamin E for 30 days compared with infected mice that consumed adequate levels of vitamin E (30 ppm)
- Application.** Eukanuba Veterinary Diets® Senior Plus, Eukanuba® Senior Formula, and Iams® Active Maturity™ Formula diets contain additional vitamin E to help maintain and enhance immunity in senior dogs.

## CHAPTER 7: SENIOR DOG CLINICAL STUDIES

Mark A. Tetrick

Pages 44-46

**Summary.** Studies in senior dogs show that body weight and other physiological and metabolic changes can impact the dogs' health and well being. A clinical study in senior dogs has shown that moderate weight reduction can significantly improve lameness scores in senior dogs with osteoarthritis (OA). Another study showed that routine screening of senior dogs can help detect unnoticed or developing medical problems. In this study, ten percent of apparently healthy older Golden Retrievers had an undetected medical condition or abnormal chemistry result that was discovered during screening.

**Findings.** **Weight loss and lameness**

- Following an initial peak when dogs are less than 2 years old, the risk of conditions involving the joints increases as dogs reach five to seven years of age and older
- Excess body weight influences the development of OA of the hip joint in humans and may do so in dogs
- Moderate weight loss in overweight senior dogs can result in a significant reduction in lameness due to hip OA
- Treatment with nonsteroidal antiinflammatory drugs may not be needed to manage lameness following successful weight loss

**Screening tests for geriatric dogs**

- Routine yearly or twice yearly screening is recommended
- Screening was used to qualify 7- to 10-year-old Golden Retriever dogs for a prospective clinical study
  - Screening consisted of physical examination, complete blood count, serum chemistry panel including total and free T<sub>4</sub> by equilibrium dialysis, urinalysis, and heartworm testing
  - Ten percent of these apparently healthy senior Golden Retrievers had an undetected medical condition or abnormal clinical chemistry result
    - Hypothyroidism was the most common unrecognized condition, present in ~6% of the screened population
    - 2% of screened dogs were heartworm positive
    - 2% of dogs screened had unrecognized renal insufficiency

**Application.** The use of diets such as Eukanuba Veterinary Diets® Nutritional Weight Loss Formula™ Restricted-Calorie™/Canine and Eukanuba Veterinary Diets® Nutritional Joint Maintenance Formulas™ Senior Plus/Canine that help attain or maintain healthy weight can help nutritionally manage lameness in senior dogs with OA. Yearly or twice-yearly screening of senior dogs with physical examinations and blood and urine testing can help identify potential health problems early.

## CHAPTER 8: NUTRITIONAL INFLUENCES ON DENTAL HEALTH

Allan J. Lepine and Edward R. Cox

Pages 47-51

**Summary.** Nutrition can play a key role in dental health. The consistency of a diet, as well as the nutritional components can affect the rate of calculus accumulation. Given that overall health problems increase with age, it is essential that not only dental but also all age-related problems be addressed on a daily basis through diet. With special care in manufacturing, mineral components can be utilized to provide daily dental benefits without altering kibble size or nutritional value. Research has shown that this approach can provide dramatic reductions in dental calculus accumulation rates. More importantly, this nutritional solution can be incorporated into a broad array of products such that any lifestyle/life stage for companion animals can be addressed along with dental concerns.

- Findings.**
- Periodontal disease is the most common diagnosis in companion animals
  - Risk appears to increase with age and decreasing body size in dogs
  - Signs of periodontal disease
    - Halitosis
    - Anorexia
    - Difficulty eating
    - Ptyalism
    - Head shaking
    - Behavioral changes
    - Red, swollen and/or bleeding gums
    - Loose teeth
    - Accumulation of plaque, calculus (tartar), and stain
    - Ulcerations on gingival or oral mucosa
  - Periodontal disease may be a risk factor for systemic disease
  - Dry food may reduce plaque and calculus vs wet food, but evidence is not conclusive
  - Rawhide and other chews may help reduce calculus, gingivitis, and alveolar bone loss
  - The standard strategy involves using mechanical scraping action to clean the teeth
    - This has primarily been achieved by changing the texture and size of the kibble
    - Only affects teeth used in chewing during chewing process
  - A new approach utilizes nutritional mineral sources in a way such that they can provide dental benefits
    - Nutritional sources of phosphates can be manipulated during manufacturing to enhance the physical properties of the kibble without altering the base formula or kibble size
    - A unique manufacturing procedure coats the polyphosphates on the outer surface of the food in a microcrystalline form
    - The polyphosphate crystals help to prevent the mineralization of plaque into calculus by forming a physical barrier on the plaque surface
    - Polyphosphates can provide whole mouth benefits as they release from the diet during mastication and carry throughout the oral cavity
    - Provides benefits to non-chewing surfaces as well as contact surfaces
    - Offers a prolonged dental benefit as the polyphosphates remain within the plaque until the body absorbs them as phosphorous nutrients
    - Dogs fed diet coated with polyphosphate microcrystals developed 55% less calculus than dogs fed the uncoated diet
    - Cats fed diet coated with polyphosphate microcrystals developed 45% less calculus than cats fed the uncoated diet

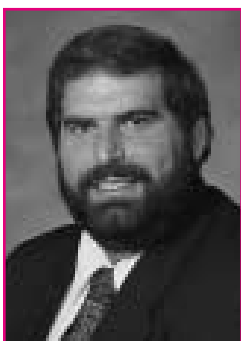
**Application.** Eukanuba Veterinary Diets® Senior Plus diet is manufactured with the new manufacturing process that allows the kibble to be coated with polyphosphate crystals that can help reduce calculus build-up during and after meals.

# Author Profiles



**Gregory F. Grauer, DVM, MS, Diplomate ACVIM**  
**Kansas State University**

Dr. Grauer received his DVM degree from Iowa State University in 1978. He then completed his postgraduate training (internship, residency, and MS degree) at Colorado State University between 1978 and 1982. Dr. Grauer received his specialty board certification in Internal Medicine in 1983. After his postgraduate training, Dr. Grauer was on the faculty at the School of Veterinary Medicine, University of Wisconsin for 7 years and then returned to the Department of Clinical Sciences at Colorado State University where he served as Professor and Section Chief of Small Animal Medicine until 2000. Dr. Grauer is currently Professor and Head of the Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University. His areas of clinical and research interest involve the small animal urinary system.



**Michael G. Hayek, PhD**  
**The Iams Company**

Dr. Hayek received a BS in Biology from Villanova University, an MS in Animal Science and a PhD in Nutritional Science from the University of Kentucky. He was a Research Associate at the Nutritional Immunology Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University where his research emphasis was the interaction between nutrition and the aging immune system. Dr. Hayek is currently Director of Strategic Research in the Research and Development Division of The Iams Company where his research interests include geriatric nutrition, longevity, and the interaction between nutrition and the immune response.



**Allan J. Lepine, PhD**  
**The Iams Company**

Dr. Lepine received his Bachelor of Science in Animal Science from Cornell University in 1980, his Master of Science in Non-Ruminant Nutrition from Virginia Polytechnic Institute and State University in 1982, and his Doctor of Philosophy in Non-Ruminant Nutrition from Cornell University in 1987. The title of his PhD thesis was Metabolic and Endocrine Factors Affecting Glucose Homeostasis in the Fasting Neonatal Pig. Dr. Lepine joined The Ohio State University in 1987 as Assistant Professor in the Department of Animal Science. His teaching and research emphasis was in non-ruminant nutrition. In 1993, he accepted a position in the Research and Development Division of The Iams Company where he is currently Principal Research Nutritionist. Dr. Lepine's current research interests include dental nutrition, puppy and kitten nutrition, skeletal health, and the effects of nutrition on reproduction in companion animals.



**Steven A. Martinez, DVM, MS, Diplomate ACVS**  
**Washington State University**

Dr. Martinez received his MS degree in Comparative Pathology in 1984 and his DVM degree in 1985 from the University of California at Davis. After completing a small animal internship at California Animal Hospital from 1985–1986 and a small animal surgical residency at Michigan State University from 1986–1989, Dr. Martinez accepted an academic appointment as Assistant Professor of Small Animal Surgery at the Atlantic Veterinary College at the University of Prince Edward Island, Canada from 1989–1990. Dr. Martinez returned to Michigan State University and served as Assistant Professor of Small Animal Surgery from 1990–1997. Dr. Martinez has been serving as an Assistant Professor of Small Animal Orthopedic Surgery at Washington State University since 1997. His current research interests include bone grafting, cytokine delivery systems in bone, and gait analysis in dogs.



**Simin Nikbin Meydani, DVM, PhD**  
**Tufts University**

Dr. Meydani is Professor of Nutrition and Immunology at Tufts University School of Nutrition Science and Policy and Tufts Sackler Graduate Program in Immunology. She also serves as Chief, Nutritional Immunology Laboratory at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts. Dr. Meydani received a PhD in nutrition from Iowa State University in 1981, an MS in nutrition from Colorado State University in 1977, and a DVM from Tehran University in 1975. Her research focuses on the impact of nutrition on the immune response and aging, as well as the effects of antioxidants and lipids. Dr. Meydani was a member of the organizing committee for the first International Aging and Immunology meeting, as well as chair and member of organizing committee for International Life Sciences Institute 1997 conference on Nutrition and Immunity. She has organized and chaired sessions of the American Aging Association and FASEB Annual Meetings. She is the recipient of several awards including the 2001 American College of Nutrition's Grace Goldsmith Award, Tufts University Outstanding Faculty Award for 1996, and 1994 HERMES Vitamin Research Award.



**Gregory D. Sunvold, PhD**  
**The Iams Company**

Dr. Sunvold received his BS in Animal Science from South Dakota State University in 1988, his MS in Ruminant Nutrition from Kansas State University in 1990, and his PhD in Nutritional Sciences from the University of Illinois in March of 1994. The title of his PhD thesis was Utilization of Selected Dietary Fibers by Dogs and Cats. In April of 1994, Dr. Sunvold joined the Strategic Research group in the Research and Development Division at The Iams Company where he is currently Director of Clinical Research. His research focus at Iams includes programs in gastrointestinal health, obesity, and diabetes. Special research interests include studying the role of dietary fiber in maintaining and enhancing the health of the dog and cat. Dr. Sunvold has published over 100 scientific papers and abstracts.



**Mark A. Tetrick, DVM, PhD**  
**The Iams Company**

Dr. Tetrick received his BS in Meat and Animal Science in 1984 and DVM in 1988 from the University of Wisconsin-Madison. After a year in large/companion animal practice, he returned to the University of Wisconsin-Madison and received his PhD in Nutritional Sciences in 1996. His thesis research dealt with utilizing medium chain triglycerides as an energy supplement for newborn animals. Dr. Tetrick joined the Strategic Research group in the Research and Development division of The Iams Company in 1996 where he is currently Research Nutritionist. His research interests include the clinical application of nutrition, with emphasis on the influence of nutrition on urinary tract health.



**David J. Waters, DVM, PhD**  
**Purdue University and Gerald P. Murphy Cancer Foundation**

Dr. Waters received his BS degree in Biological Sciences from Cornell University in 1980 and his DVM degree from Cornell in 1984. In 1989, he completed a residency in Small Animal Surgery at the University of Minnesota and in 1990 he became a Diplomate of the American College of Veterinary Surgeons. In 1992, he received the PhD degree in Veterinary Surgery from the University of Minnesota. Dr. Waters joined the faculty of the Department of Veterinary Clinical Sciences at Purdue University in 1991 as Assistant Professor of Surgery and was promoted to Associate Professor in 1996. In 2000, he was appointed Executive Director of the Gerald P. Murphy Cancer Foundation, a non-profit organization which supports and conducts basic, comparative, and clinical research. In 2001, he was promoted to Professor of Surgery and Comparative Oncology at Purdue University. Dr. Waters currently serves as the Co-director of the Purdue Comparative Oncology Program and Associate Director of the Purdue Gerontology Program. Dr. Waters' research has focused on the comparative aspects of prostate cancer and skeletal neoplasms. His current research is in the evaluation of novel anticancer therapies, strategies for cancer prevention, and biomarkers of mammalian aging and cancer risk.

# Cancer in the Elderly Dog

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## INTRODUCTION

Cancer is one of the most prevalent and life-threatening diseases affecting elderly pet dogs. The purposes of this paper are to (1) explore how aging influences the risk for cancer as well as the histologic spectrum and biological aggressiveness of resultant cancers, (2) evaluate some of the important considerations in the treatment of cancer in elderly dogs, and (3) outline principles of cancer prevention which might be exploited to reduce cancer-related mortality. This discussion provides the rationale for the design of future studies to determine if nutritional intervention during the life course can significantly reduce cancer incidence or cancer-related mortality in elderly dogs.

## CANCER AND AGING

The association between aging and cancer is compelling enough for one author to formally consider gerontology as oncology.<sup>1</sup> Conceptually, the association between aging and cancer can be dichotomized as follows: (1) the influence of aging on cancer risk and (2) the influence of aging on the biological behavior of resultant cancers. Profound breed-specific differences in canine life span make it challenging to reliably analyze the relationship between host age and cancer development in pet dogs. In order to analyze how aging influences cancer risk or prognosis, we

developed a method to standardize the chronologic age of short-lived and long-lived breeds.<sup>2</sup> This algorithm has been used to compare age at bone tumor diagnosis in small versus large breed dogs<sup>3</sup> and to compare age at prostate cancer diagnosis in men versus pet dogs.<sup>4</sup>

## THE CANCER CELL: AUTONOMOUS VILLAIN OR ULTIMATE PARASITE?

Host:tumor cell interactions are important determinants of tumor cell behavior.<sup>5</sup> The hallmark of cancer is the ability of transformed cells to escape normal growth regulatory constraints, invade adjacent tissue compartments, and successfully spread to distant target organs. The aggressive behavior of cancer cells reflects their genetic alterations, or “hits”, as well as their ability to usurp host factors. The previously held perception of a cancer cell as a hardwired, programmed robot has given way to a more contemporary view of the cancer cell as a highly interactive and successful parasite. Host:tumor cell interactions regulate virtually every aspect of tumor cell behavior, from growth and metastasis<sup>6</sup> to sensitivity to chemotherapeutic agents.<sup>7-9</sup>

These observations have important implications. Aging-related changes in homeostasis within host tissues may significantly impact the risk for development of lethal cancers. This raises important questions. Does the *in vivo* accumulation of senescent cells in elderly hosts contribute to an increased risk for cancer development? Furthermore, can age-related changes that favor cancer development be modified by interventions, including dietary modification?

## OLD HOSTS ARE CANCER SUSCEPTIBLE

In humans, the risk for most adult-onset cancers increases dramatically with increasing age. **Figure 1** shows that for 12 major cancers, more than 50% of cases are diagnosed in elderly individuals over 65 years of age.<sup>10</sup> Although data from pet dogs are less complete, a similar age-associated increase in cancer risk appears to exist within the pet dog population. For example, testicular cancer is rarely diagnosed in dogs less than 6 years of age (**Figure 2**).<sup>11</sup>

Experimental evidence also supports the hypothesis that a host's susceptibility to develop cancer is age-dependent. In an important study by McCullough et al. (1997), young (3–9 months old) and old (18–24 months old) Fischer 344 rats received implantation of BAG2-GN6TF transformed rat epithelial cells into their liver.<sup>12</sup> On day 7 after tumor cell implantation, the incidence of tumors in both young and old rats was 100%. However, on day 85 post-implantation, all of the tumors had regressed in young rats, while tumors were present in 17 of 19 (89%) old rats. The striking age-dependent regression of BAG2-GN6TF liver tumors in this study clearly demonstrates that the old host provides an environment that is in some way better suited for the survival and proliferation of tumor cells.

Why are old tissues vulnerable to cancer development? Should we blame it on *old cells*? Perhaps the late onset of adult

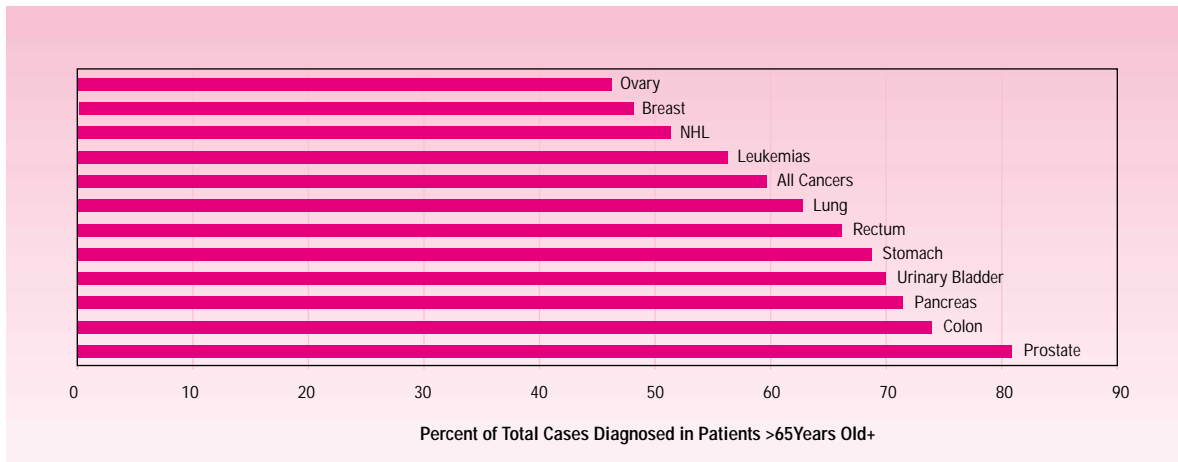


Figure 1. Aging significantly influences risk for cancer development. Modified from Yancik R (reference 10).

cancers which commonly occur in pet dogs and humans simply reflects a time-related accumulation of DNA damage in cells which ultimately leads to malignant transformation and cancer development. Should we blame it on *old tissues*? Accumulating evidence suggests that this may be a more accurate indictment. The decisions that cells make (ie, proliferation, apoptosis, differentiation) are highly contextual.<sup>13</sup> That is, an epithelial cell's behavior (phenotype) depends upon that cell's interactions with neighboring epithelial cells, stromal cells, and extracellular matrix (Figure 3). In fact, the manner in which a cell that has sustained a genetic "hit" manifests that insult may depend upon the permissiveness of normal cells in the tissue micro-environment.<sup>14</sup> This raises the intriguing possibility that the integrity of neighboring stromal cells in young and elderly hosts may be a key determinant of whether foci of transformed epithelial cells progress to clinically important cancers.<sup>15</sup>

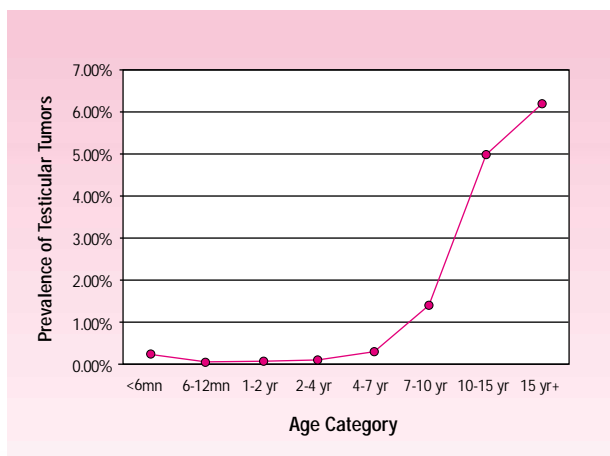


Figure 2. Age-specific prevalence of testicular tumors in 458,415 non-cryptorchid male dogs.

## HOST AGE INFLUENCES THE BIOLOGICAL BEHAVIOR OF TUMORS

Data from humans and experimental tumor models suggest that host age may influence the biological behavior of malignant tumors.<sup>16</sup> It has been observed that certain tumors behave more aggressively in young adults, in contrast to the more indolent clinical course of these tumors in elderly hosts.<sup>17</sup> In an effort to determine if host age influences the development of prostate carcinoma skeletal metastases, we compared age at prostate cancer diagnosis in 29 dogs with skeletal metastases to age at prostate cancer diagnosis in 79 dogs *without* skeletal metastases.<sup>18</sup> In dogs with prostate carcinoma, young dogs had a greater likelihood of skeletal metastases at time of cancer diagnosis than older dogs ( $P=.03$ ). Dogs in the youngest quartile for physiologic age were 4.9X more likely to have skeletal metastases than dogs in the oldest quartile. These data support the hypothesis that host age may significantly influence the biological behavior of spontaneous prostate carcinoma in pet dogs.

The host:tumor cell interactions that influence the lethality of cancers are likely to be complex and reciprocal. Not surprisingly, the mechanisms responsible for the association between young host age and biological aggressiveness of cancers have not been determined. According to one theory, cytokines that drive tumor cell proliferation may be more abundant in young hosts.<sup>19</sup> Experimental data suggest that the enhanced capacity of young hosts to support neoangiogenesis might also contribute to the increased aggressiveness of tumors in young hosts. Subcutaneous injection of B16-F10 melanoma cells in young (2-month-old) and old (16-month-old) C57/BL mice resulted in significant age-related differences in tumor size and tumor angiogenesis.<sup>20</sup> Tumors in young mice were about 50% larger and had increased tumor vascularity. In a series of dogs with prostate carcinoma,<sup>18</sup> we determined if age-related differences in tumor angiogenesis were significantly associated with risk for skeletal metastases. We found that the microvessel density

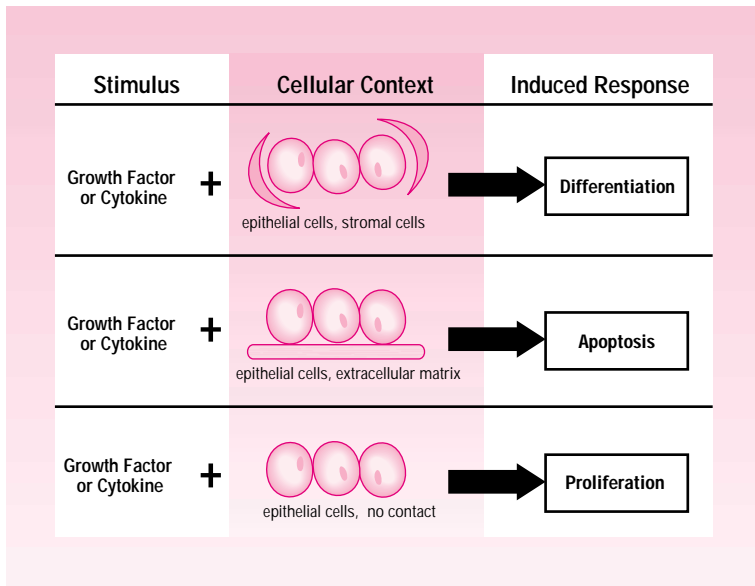


Figure 3. The response of a tumor cell to a hypothetical stimulus is highly dependent upon cellular context.

of primary tumors, an index of tumor angiogenesis, was not predictive of likelihood of skeletal metastases in dogs with prostate carcinoma. Clearly, additional studies using pet dogs with naturally-occurring malignancies are warranted to further investigate the biological basis for the “young host — aggressive cancer” phenomenon.

## DIFFERENCES IN THE HISTOLOGIC SPECTRUM OF CANCERS IN YOUNG VERSUS OLD HOSTS

The histologic types of neoplasms that commonly affect young people (< 30 years old) differ significantly from those that affect older adults. Tumors of the hematopoietic system, testis, and central nervous system are overrepresented in young people.<sup>21</sup> In a study of neoplasms affecting young dogs < 6 months of age, the three most common sites were hematopoietic system, brain, and skin.<sup>22</sup> The relative risk (and 95% confidence interval) for tumors of the hematopoietic system or brain in dogs < 6 months of age was 10.9 (4.1–28.9) and 3.3 (1.4–7.4) respectively, compared to mature dogs.<sup>22</sup>

From these data, it is reasonable to propose that dogs and people share certain genetic or environmental factors that confer susceptibility to the development of particular tumors early in life. Aging in both species apparently modifies the histologic spectrum of resultant tumors. The risk for benign (hemangioma) versus malignant (hemangiosarcoma) vascular tumors in pet dogs is significantly influenced by aging.<sup>23</sup> Overall, vascular tumors of young dogs were 4X more likely to be benign than vascular tumors that developed in elderly dogs. Interestingly, our data suggest that the influence of aging on vascular tumor risk may be breed-specific, with striking differences between Golden Retrievers and Boxers.

## CANCER RESISTANCE IN THE OLDEST-OLD

Although cancer is a disease strongly associated with aging, age-specific cancer mortality rate begins to decline in the tenth decade of life (Figure 4).<sup>24</sup> Interestingly, data from human centenarians suggest that the oldest-old humans seldom develop lethal cancers.<sup>25</sup> Studies in our laboratory suggest a similar decline in the percentage of very old dogs that succumb to cancer. Taken together, this raises the possibility that cancer resistance genes are overrepresented in the oldest-old, where they may influence longevity by protecting the host from malignant disease.

The nature of the “cancer resistance” of the oldest-old has not been well defined. Cancer resistance in the oldest-old may reflect a universal resistance of the host’s cells to malignant transformation, either through efficient DNA repair or by mechanisms that protect cells from exposure to DNA damaging agents. Alternatively,

there may be widespread transformed foci that remain dormant and clinically undetectable in individuals that are cancer resistant. A third possibility is that cancer-resistant individuals develop benign neoplasms or non-lethal malignancies and therefore their resistance is a manifestation of the development of tumors with much more “tame” biological behavior.

## OPTIMIZING THE TREATMENT OF CANCER IN THE ELDERLY PATIENT

Elderly patients frequently suffer from concurrent diseases. Common conditions, such as renal or cardiac insufficiency, may render certain treatment options unacceptable. For example, doxorubicin may be contraindicated for

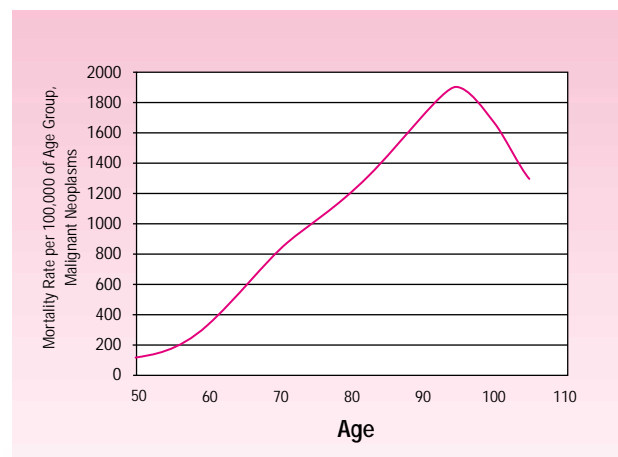


Figure 4. Mortality rates from all malignant neoplastic diseases for age groups 50-100+ in 1990 based on vital statistics of the United States. (Modified from Smith DWE, reference 24.)

the treatment of cancer in dogs with cardiac disease. Similarly, forequarter amputation may be contraindicated for treatment of osteosarcoma of the distal radius in a dog with severe degenerative joint disease of the stifle.

The results of a recent survey of veterinary practitioners emphasized the importance of nutrition in optimizing the medical care of elderly dogs. In that study, nutrition was considered one of the most important areas where more research is needed to improve the quality of geriatric veterinary medicine.<sup>26</sup>

Current clinical practice dictates that selection of cancer treatment in pet dogs is largely based upon the patient's tumor type and the prior experience of the veterinarian. In the future, the molecular signature of the patient's tumor will be determined so that *treatment based upon tumor type will be superseded by treatment based upon the patient's tumor*. It will be important to establish how strongly the tumor's expression of particular molecules can predict outcome. To this end, tumor markers will be sought that correlate with likelihood of primary tumor control, presence or absence of micrometastatic disease, rapidity of disease progression, or response to particular treatments.

In terms of treatment objectives, it should be noted that cancer is one of the few chronic diseases that veterinarians and physicians attempt to cure. A diagnosis of diabetes mellitus triggers a vigorous attempt to control or ameliorate the disease, not an attempt to cure. The clinical and scientific community has begun to seriously question whether cancer control seems to make more sense than cancer eradication as a treatment goal. Non-cytotoxic interventions intended to suppress tumor cell proliferation or to render tumor cells clinically harmless by depriving them of blood supply are under intense investigation. Numerous dietary constituents can favorably modify cellular processes which are integral to the progression of early cancers to life-threatening disease. For this reason, it is reasonable to predict that dietary interventions will be evaluated as new approaches to achieve cancer suppression.

## EFFECTIVE CANCER PREVENTION

Effective cancer prevention, rather than cancer treatment, may hold the most promise in our quest to reduce significantly the number of cancer-related deaths. At least two ingredients are critical to a successful cancer prevention strategy: (1) development of a non-toxic chemoprevention strategy, and (2) the identification of a practical target population. Successful chemoprevention strategies utilize agents that can block or delay one or more of the critical processes in multistep carcinogenesis. The ideal target population consists of a subpopulation at high risk for a particular tumor. This emphasizes the need for carefully designed epidemiologic studies to generate population-based data on cancer risk within the pet population.

Cancer preventive strategies could have a significant impact on cancer-related mortality if a reduction in cancer

incidence can be achieved. Alternatively, a goal of these strategies might be to increase the likelihood that the cancers which develop are organ-confined, non-metastatic, and therefore highly curable by surgery alone.

## IDENTIFICATION OF A HIGH RISK COHORT FOR CANCER PREVENTION: Genetic Constitution, Environmental Exposure, and Cancer Risk

Gene-environment interactions determine an individual's risk for cancer development. Certain aspects of cancer risk may be age-dependent. For example, age-dependent changes in the immune system or within a particular tissue may render the elderly host more vulnerable to cancer. In contrast, familial patterns of cancer susceptibility are often attributable to inherited germ line mutations within a few major tumor suppressor genes.<sup>27,28</sup> In the human population, molecular epidemiologists are now diverting their attention to the vast number of polymorphisms in genes that encode for enzymes that regulate carcinogen activation and detoxification<sup>29</sup> and steroid hormone metabolism.<sup>30</sup> Profound inter-individual differences in these enzyme systems mean that individuals exposed to the same environmental dose of a carcinogen (eg, environmental tobacco smoke) actually receive very different biological doses of that agent. Host cells receiving the highest biological dose are at high risk for mutations associated with cancer initiation and progression. These genetic polymorphisms likely account for a considerable number of the non-familial, so-called "sporadic" cancers within the human population. Undoubtedly, a molecular epidemiological approach will produce new insights into the identification of the subpopulation of pet dogs at highest risk for cancer. These efforts will lead to the validation of integrated biomarkers of cancer risk that will help to make practical cancer prevention in pet dogs possible in the near future.

*Results of a recent survey of veterinary practitioners emphasized the importance of nutrition in optimizing the medical care of elderly dogs.*

## IMPLICATIONS OF MULTISTEP CARCINOGENESIS: EARLY LIFE EVENTS SIGNIFICANTLY INFLUENCE CANCER RISK

Are elderly dogs the most appropriate targets for cancer prevention interventions? Perhaps not. Most carcinomas are believed to develop through a multistep process of epithelial carcinogenesis. This process may require a considerable duration of time. For example, most human breast and

prostate carcinomas are believed to develop over a 20 to 25 year period,<sup>31</sup> representing about 30% of average life expectancy. It is also apparent that different factors may be important contributors to early phases (ie, initiation) or late phases (ie, promotion and tumor progression) of cancer development. Thus, it may be prudent to direct cancer prevention strategies toward young adults rather than the elderly. Elimination of exposures early in life have important impact on cancer risk later in life. For example, the protective effect of ovariectomy on the subsequent development of mammary cancer in dogs is well documented.<sup>32</sup> Diet and body conformation early in life may also influence mammary cancer risk.<sup>33,34</sup> The lack of protection afforded by late ovariectomy emphasizes that the efficacy of any strategy may be highly dependent upon the timing of the intervention.

## SUMMARY

Experts in the osteoporosis field recognize that the risk for post-menopausal osteoporosis in older women is highly dependent upon the peak bone mass achieved in adolescence. Similarly, an insightful approach to cancer risk and prevention must rely upon a life course perspective. Cancer preferentially affects the elderly, but meaningful progress in the reduction of cancer incidence will likely rely upon prevention strategies targeted to young adults at high risk for cancer development. The treatment of cancer in elderly dogs presents unique challenges. The ability to treat the patient's tumor on the basis of its molecular signature will likely lead to improved prognosis for elderly dogs with cancer.

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# Nutritionally Managing Glucose Metabolism in the Senior Dog and Cat

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## INTRODUCTION

Not only does a large population of senior canines and felines exist, but the desire of owners to keep their senior dogs and cats in optimal health appears to be increasing. Thus, understanding physiological changes that occur in individuals during the aging process can help meet the goal of improving seniors' health. One such physiological change that may not be recognized during routine clinical evaluation is related to glucose metabolism.

## CHANGES IN GLUCOSE METABOLISM WITH AGING

Although extensive physiological information is known about production animal species (ie, cattle, pigs, sheep, poultry), little information is known regarding changes in glucose metabolism of these species with age. Thus, most information about age-related changes in glucose metabolism has been from research in humans. These findings indicate a decline in glucose tolerance with age<sup>1</sup>; as a consequence, it is thought that maintaining normal glucose metabolism as the individual ages may promote longevity.

Sheffy et al.<sup>2</sup> studied the blood glucose response to an oral dose of glucose (1 g/kg of body weight). Although no statistically significant results were found, these results were interpreted to indicate that delayed glucose absorption occurred in adult, senior dogs compared to adult, young dogs. We have recently conducted an experiment to gain a better understanding of the glucose and insulin response to the meal in the canine.<sup>3</sup>

In contrast to Sheffy et al.,<sup>2</sup> we measured the glycemic response to a complete meal rather than an oral dose of glucose. As with Sheffy et al.<sup>2</sup> we found senior dogs have delayed glucose absorption compared with young dogs (**Figure 1**). This could be due to: 1) delayed gastric passage, 2) delayed glucose absorption, 3) delayed nutrient digestion, or 4) a combination of any of these effects. However, our findings with insulin (not measured by Sheffy et al.<sup>2</sup>) are intriguing as they indicate a much greater secretion needed in older dogs. This implies that insulin sensitivity is reduced in these animals. Further work is needed to better understand why glucose metabolism occurs in this fashion with aging in dogs. However, these results clearly indicate that differences in glucose metabolism exist between the senior and young adult dogs.

Changes in aging due to glucose metabolism also appear to be evident in the cat as well. In a study reported by Massimino et al.<sup>4</sup> the effect of age was evaluated by

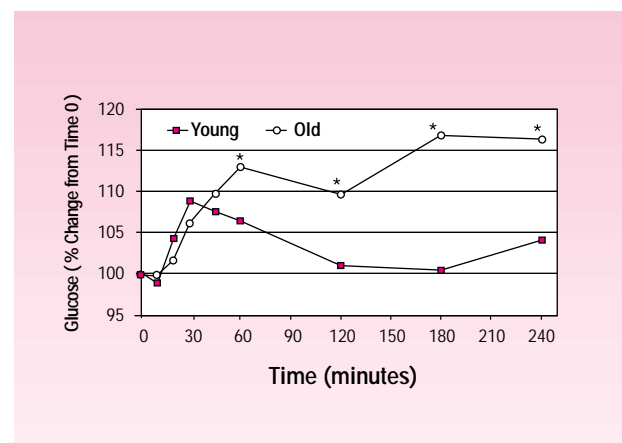
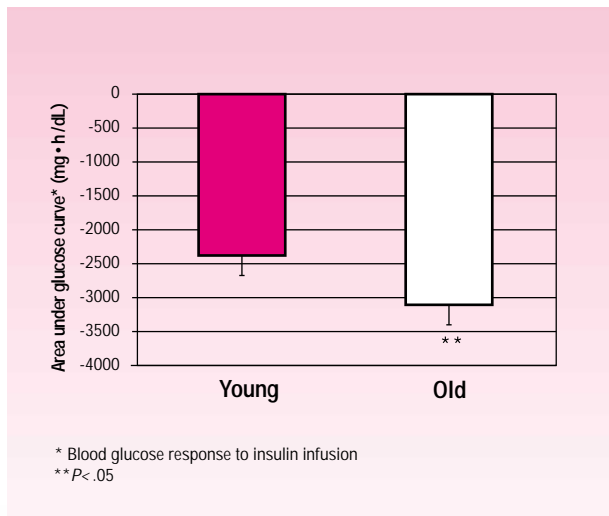


Figure 1. Aging changes the glucose response in dogs. \*Represents significantly different values ( $P < .05$ ).

conducting a glucose tolerance test on 20 young compared to 20 old cats. Young cats had higher glucose effectiveness compared to older cats. Further, the older cats had a greater area above the glucose curve and under baseline after an insulin tolerance test than the younger cats (**Figure 2**). These results indicate a reduced ability of older cats to remove glucose from the blood compared to younger cats.



**Figure 2.** Aging in cats decreases the ability of insulin to dispose of glucose. From reference 4.

The relationship between increased body fat and altered glucose metabolism in the human is well accepted.<sup>5</sup> A similar phenomenon in dogs is partially supported by the results from Rocchini et al.<sup>6</sup> who found increased insulin resistance in dogs with increased body weight after consumption of a diet supplemented with fat. Insulin resistance is considered to be the most common abnormality associated with central abdominal or visceral obesity in humans.<sup>7</sup> Thus, body composition appears to be associated with changes in glucose metabolism. Current studies indicate that increased adiposity occurs with aging in senior dogs and cats.<sup>3,4</sup> It is plausible that increased adiposity and/or increased abdominal fat distribution are responsible for the changes in glucose metabolism that occur with age. Regardless of the metabolic reason, clinical management of glucose metabolism in dogs and cats could result in improved health.

## NUTRITIONAL CONCEPTS FOR IMPROVING GLUCOSE METABOLISM

To date, the primary nutritional concept that has been implicated for improving glucose metabolism has been the use of high-fiber diets. At times, benefits have been realized through this approach. However, concerns about side effects associated with high-fiber diets in dogs and cats have also been noted. These include: 1) decreased palatability, 2) decreased nutrient digestibility, 3) decreased skin and

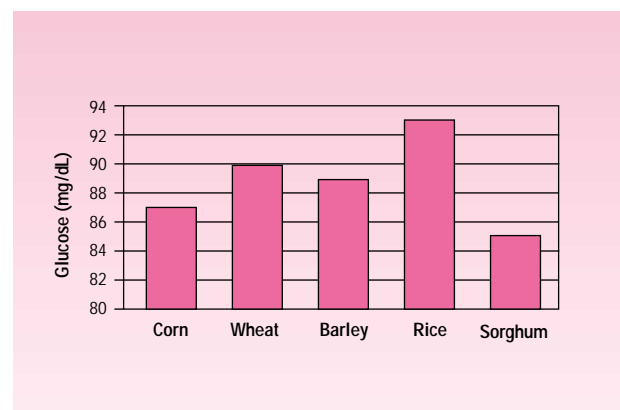
haircoat quality, 4) increased constipation and/or increased frequency of defecation, and 5) poor mineral balance. Thus, alternative nutritional approaches for improving glucose metabolism have warranted exploration. We have been very interested in this area and as such will summarize some of the latest research that may improve glucose metabolism of dogs and cats.

## Starch

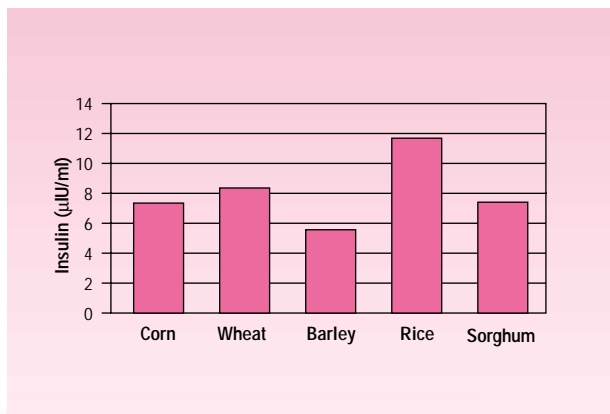
A “glycemic index” table has been developed that compares different cereal grain sources of starch and their influence on the glycemic response to a meal in humans.<sup>8</sup> Fifty percent or more of the calories that are consumed on a daily basis can come from carbohydrates. Since most food carbohydrates are directly broken down into glucose, their influence on glucose metabolism can be substantial.

We were also interested in this phenomenon as it relates to dogs and cats. Therefore, an experiment was conducted with dogs to evaluate the influence of starch source on postprandial glycemic response.<sup>9</sup> In this experiment five diets were fed that only varied in their starch source. Results indicated that the source of starch influenced both the glucose and insulin response to a meal. Both glucose and insulin response were greatest when dogs consumed rice as their starch source (**Figures 3 and 4**). The glucose response was minimized when the sorghum was consumed by the dogs (**Figure 3**) while the insulin response was minimized when the barley was consumed (**Figure 4**). Thus, a combination of sorghum and barley as the carbohydrate source appears to be most effective in reducing the glycemic response to a meal in the canine.

In another experiment with cats, the influence of starch source on glycemia was evaluated.<sup>10</sup> Results indicated that the physiological effect of starch sources is not uniform with regard to the postprandial glucose and insulin response



**Figure 3.** Average postprandial glucose response to selected starch-containing diets (Average = average of baseline, 10, 20, 30, 45, 60, 120, 180, and 240 minute samples) fed to dogs. (Used with permission. Originally published in Sunvold GD, Bouchard GF. The glycemic response to dietary starch. In: Reinhart GA, Carey DP, ed. Recent Advances in Canine and Feline Nutrition, Vol. II: 1998 Iams Nutrition Symposium Proceedings. Wilmington, OH: Orange Frazer Press, 1998; 123-131.)



**Figure 4.** Average postprandial insulin response to selected starch-containing diets (Average = average of baseline, 10, 20, 30, 45, 60, 120, 180, and 240 minute samples) fed to dogs. (Used with permission. Originally published in Sunvold GD, Bouchard GF. The glycemic response to dietary starch. In: Reinhart GA, Carey DP, ed. Recent Advances in Canine and Feline Nutrition, Vol. II: 1998 Iams Nutrition Symposium Proceedings. Wilmington, OH: Orange Frazer Press, 1998; 123-131.)

in cats. Taken together, the glucose and insulin response of cats appears to be exacerbated in cats fed a rice-containing diet compared to a diet that contains starch sources such as corn, barley or sorghum. Thus, results from both dogs and cats suggest that the starch source is important in older animals since their glucose metabolism is generally different than younger animals.

### Carboxymethylcellulose

Carboxymethylcellulose (CMC) consists of cellulose modified to enhance its viscosity. This fiber source is primarily thought to effect glycemia through its ability to slow glucose absorption since it is viscous. Also, CMC is relatively low in fermentability so it is fairly resistant to the actions of intestinal bacteria (unpublished data). A similar viscous fiber, hydroxypropylmethylcellulose has been reported to decrease postprandial blood glucose in noninsulin dependent diabetic humans.<sup>11</sup> Thus, it was of interest to evaluate the influence of CMC on the postprandial glucose response by dogs.

In this study, diets containing either no CMC or 1% low-viscosity CMC, 1% high-viscosity CMC, 3% low-viscosity CMC, or 3% high-viscosity CMC were fed to healthy dogs.<sup>12</sup> Blood glucose and insulin values were obtained at several times during the 8 hours following ingestion of the meal. Results indicated that 1% high-viscosity CMC added to the diet reduced postprandial blood glucose but had little influence on postprandial blood insulin levels. Thus, proper diet viscosity may blunt the rise in blood glucose immediately following a meal.

### Fermentable Fibers

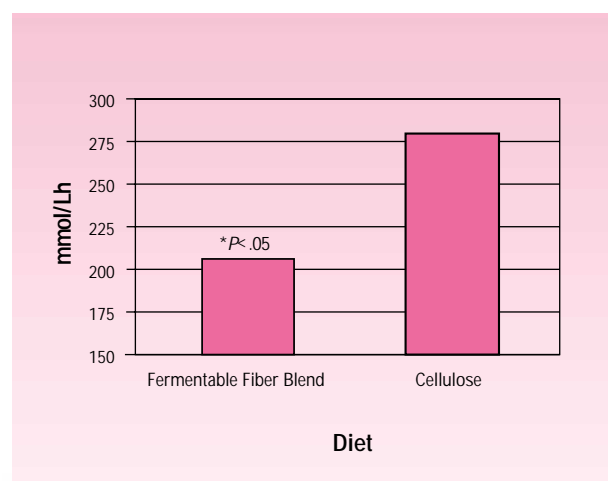
Certain fibers may also have a benefit for animals with reduced insulin-secreting abilities or to improve the timing of insulin secretion.<sup>13</sup> The effect of fibers that are fermentable

was evaluated for their ability to improve glucose storage through increased availability of insulin. Dogs were fed either a nonfermentable diet (cellulose) or a fermentable fiber blend (beet pulp, gum arabic, and fructooligosaccharides). The fermentable fiber blend contained fiber sources that are fermented by anaerobic bacteria in the intestine. That is, beet pulp, gum arabic, and FOS are all moderate to moderately high in fermentability whereas cellulose is poorly fermented.<sup>14-16</sup> Fermentation of fiber produces short-chain fatty acids (SCFA) that stimulate intestinal cells to produce proglucagon. Proglucagon is later cleaved to release glucagon-like peptide (GLP). Glucagon-like peptide-1 is a potent insulin secretagogue. This study demonstrated that chronic feeding of a diet containing a fermentable fiber blend increased blood GLP-1 and insulin levels after an oral glucose load (presumably through increased secretion of insulin from the pancreas). This resulted in a lower rise in blood glucose levels (Figure 5).

### Chromium Tripicolinate

Chromium tripicolinate (ie, chromium picolinate) is a bioavailable form of chromium.<sup>17</sup> It has been evaluated in several species for its effects on improving blood glucose metabolism.<sup>18-21</sup> However, little is known about glucose metabolism of dogs and cats as influenced by dietary chromium. Therefore, it was of interest to evaluate the ability of chromium to improve glucose metabolism in these animals.

Two separate experiments with healthy dogs were conducted and the results pooled.<sup>22</sup> Results indicated that 300 ppb supplementation of chromium in the form of chromium



**Figure 5.** Incremental area under the curve for glucose following an oral glucose tolerance test in dogs after consuming a diet containing either cellulose or a fermentable fiber blend. (Used with permission. Originally published in McBurney MI, Massimino SP, Field CJ, Sunvold GD, Hayek MG. Modulation of intestinal function and glucose homeostasis in dogs by the ingestion of fermentable dietary fibers. In: Reinhart GA, Carey DP, ed. Recent Advances in Canine and Feline Nutrition, Vol. II: 1998 Iams Nutrition Symposium Proceedings. Wilmington, OH: Orange Frazer Press, 1998; 113-122.)

tripicolinate improved ( $P < .08$ ) the ability of dogs to clear glucose from their blood (**Figure 6**). It has been suggested that chromium is an essential component of glucose tolerance factor.<sup>17</sup> Glucose tolerance factor is hypothesized to potentiate the action of insulin. Potentiation of insulin's effect would indirectly aid glucose clearance from the blood by improving glucose storage in muscle. Another experiment with senior dogs supports this idea. In this experiment, insulin sensitivity appeared to increase greater than 20% with 300 ppb chromium supplementation (Hayek and Sunvold, unpublished data, 1998). An experiment with cats was recently conducted by Appleton et al. to evaluate the effect of chromium on glucose tolerance in these animals.<sup>23</sup> This study evaluated the effect of increased levels of chromium (0, 150, 300, and 600 ppb supplemental chromium) in the form of chromium tripicolinate to alter glucose and insulin metabolism. Results from this study indicated a dose-dependent effect of chromium on parameters associated with improving glucose metabolism.

A side benefit of chromium supplementation to felines appears to be an improved body composition in cats during weight loss.<sup>24</sup> This experiment evaluated the effects of feeding diets supplemented with 0, 300, and 600 ppb of chromium tripicolinate on body compositional changes during rapid weight loss in cats. Dual energy x-ray absorptiometry (DEXA) indicated that percent lean body mass loss (0 ppb = 19.6, 300 ppb = 16.5, 600 ppb = 15.6) was decreased after 19 weeks of consuming chromium-supplemented diets, suggesting that weight loss experienced in cats consuming chromium-supplemented diets was due to fatty tissue degradation not to muscular atrophy. The numerical decrease in fat mass,

observed in cats fed supplemental chromium, further supports the previous observation. These findings indicate that during weight loss, chromium supplementation to cats can aid in preserving lean body mass at the expense of fat. In the case of a diabetic, an improvement in muscle mass at the expense of fat mass would generally be considered beneficial since adiposity may be associated with insulin resistance.<sup>25</sup>

## Carnitine

L-Carnitine is a vitamin-like compound that helps the body metabolize fatty acids through increasing beta-oxidation within the mitochondria. L-Carnitine attaches to fatty acids, transporting them to the mitochondria where they are broken down via oxidation and converted to energy. As stated earlier, increased body fat tends to occur with aging and is also associated with decreased glucose metabolism. Therefore, nutrients that help reduce body fat could indirectly improve the status of a senior's glucose metabolism.

In dogs, diets supplemented with L-carnitine resulted in greater loss of fat mass compared to diets that were not supplemented.<sup>26,27</sup> Similar results in cats were obtained in research conducted by Center et al.<sup>28</sup> Thus, the use of carnitine when supplemented to weight loss diets of dogs and cats has been demonstrated to promote fat metabolism.

## RECOMMENDATIONS

Research to date suggests that aging alters glucose metabolism. Several nutritional concepts have recently come available that promote improved glucose metabolism. These include: 1) sorghum and barley as carbohydrate sources; 2) a viscous fiber, CMC; 3) a fermentable fiber blend; 4) chromium tripicolinate; and 5) carnitine. By utilizing diets that incorporate these concepts, one can help meet the goal of improving glucose metabolism in senior animals.

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**Figure 6.** Effect of supplemental dietary chromium on glucose clearance rate in dogs. (Used with permission. Originally published in Spears JW, Brown TT Jr, Sunvold GD, Hayek MG. Influence of chromium on glucose metabolism and insulin sensitivity. In: Reinhart GA, Carey DP, ed. *Recent Advances in Canine and Feline Nutrition, Vol. II: 1998 Iams Nutrition Symposium Proceedings*. Wilmington, OH: Orange Frazer Press, 1998; 103-112.)

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# Nutrition and Aging in Companion Animals

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## INTRODUCTION

Similar to human populations the proportion of senior companion animals is significant. For example, it has been noted that in the United States there are 7.3 million dogs and 6 million cats over the age of 11.<sup>1</sup> This has led to an increased interest in nutritional care of senior dogs and cats. In order to evaluate how to care for this life stage, one must develop an understanding of gerontology in companion animals. Gerontology has been defined as “the scientific study of aging and the aged through the integration of disciplines involving both biological and behavioral sciences.”<sup>2</sup> It is important to note that the aging process is a series of stages that begins with conception, continues through maturation, adulthood and senescence (geriatric), and ends with death.<sup>3</sup> Therefore, the study of gerontology is a study of life processes that influence the final stage (ie, geriatric stage) of the animal’s life.

A first step to understanding this life stage is to determine at what age dogs and cats are considered senior or geriatric. This is especially true for the dog since body size correlates to the anticipated life expectancy for a breed.<sup>4</sup> Based on surveys to veterinary clinics, which asked the question at what age their patients showed geriatric diseases, Goldston proposed the breakdown presented in **Table 1**.<sup>5</sup> However, as mentioned earlier, aging is a continuous process so we need to consider influencing these animals prior to the onset of age associated diseases. This has led to the development of age charts, such as the one presented in **Table 2**, which divides the older life stage into senior and geriatric, with adjustments for various breed body sizes.

Table 1. Ages dogs and cats start showing diseases associated with aging. Adapted from reference 5.

Classification	Weight (lb)	Age (yr)
Small Dogs	0 – 20	11.48 ± 1.85
Medium Dogs	21 – 50	10.90 ± 1.56
Large Dogs	51 – 90	8.85 ± 1.39
Giant Dogs	> 90	7.46 ± 1.94
Cats		11.88 ± 1.94

A second step for understanding this life stage is to realize the physiological changes that occur during aging in the dog and cat. There has been increased research over the past decade defining the changes that occur with aging in the dog and cat.<sup>5,6</sup> This has led to the development of nutritional strategies to match these age-associated changes. This paper will review a few of these changes and how nutrition may play a role.

## THEORIES OF AGING

A variety of theories of aging have been proposed over the years.<sup>7</sup> Some theories attribute the aging process to genetic controls. These theories include explanations such as codon restriction, somatic mutation, and gene regulation. Other theories describe aging as a gradual loss of homeostasis in certain physiological systems such as the immune system or the neuroendocrine system. Still other theories state that aging is due to an accumulation of detrimental products such as lipofuscin or free radicals. Unfortunately, none of these theories have completely explained the mammalian aging process. It is generally thought that aging is a multifactorial phenomena that includes various aspects of each of these theories. It is interesting to note that while some of these theories are due to inevitable changes that are results of physiological aging, others result from an accumulation of metabolic products over time. Therefore, anti-aging strategies should focus on both preventing the accumulation of detrimental products as well as adjusting to inevitable physiological changes.

**Table 2. Age analogy chart (Chart developed jointly by W.D. Fortney, DVM and R.T. Goldston, DVM, DACVIM, DABVP; used with permission)**

Age (in years)	Canine Adult Size (in pounds)			
	0-20	21-50	51-120	>120
3	28	29	31	39
4	32	34	38	49
5	36	39	45	59
6	40	44	52	69
7	44	49	59	79
8	48	54	66	89
9	52	59	73	99
10	56	64	80	
11	60	69	87	
12	64	74	94	
13	68	79		
14	72	84		
15	76	89		
16	80	94		
17	84			
18	88			
19	92			
20	96			

**Key:**  
 Adult   
 Senior   
 Geriatric

Several of these theories may interact with nutrient metabolism. For example, the immunological theory of aging states that certain aspects of aging may result from the dysregulation of the immune system as animals age. The interaction between nutrition and the immune system has received much attention recently and nutrients such as vitamin E may aid the aging immune response.<sup>6,8</sup> Another example would be the free radical theory of aging, which proposes that the aging process results in an accumulation of free radicals which may cause intracellular damage leading to degenerative diseases associated with aging. The interaction between antioxidant nutrients and free radicals has also been an area of interest, which may play a role in the aging process. The association between these theories

and nutrition emphasizes the need to consider optimal nutritional interventions in the geriatric patient.

## NUTRIENT ABSORPTION AND UTILIZATION

When considering nutrition for a particular life stage one must consider both nutrient absorption and nutrient utilization. The effect of age on intestinal absorption of nutrients has been examined in the dog.<sup>9</sup> In this study, nutrient balance experiments were conducted on young and old Beagles to determine any age-related changes in protein, fat, energy, vitamin, and mineral absorption. It was demonstrated that there were no age-related changes in absorption of these nutrients. This same observation has also been noted in other species as well and thus may be due to the ability of the gastrointestinal tract to compensate for small decreases in absorptive efficiency. Therefore, recommendations of age-related nutrient requirements may not be warranted when based solely on impaired nutrient absorptive capacity.

Although nutrient absorption may not change significantly with age, there are indications of progressive age-related changes in nutrient utilization in geriatric populations. Defining and understanding these alterations will help to design specific diets to meet the needs of the older animal.

### Glucose

It has been reported that aging humans and primates have a dysregulated glucose metabolism.<sup>10-12</sup> This has led to the emergence of the “Glycosylation Theory of Aging” which states that excess (free) sugars nonenzymatically react with biological proteins to form advanced glycation end (AGE) products.<sup>13,14</sup> The accumulation of these AGE products have been implicated in contributing to several pathological conditions associated with aging such as cataracts, atherosclerosis, Alzheimer’s disease, and stroke. This decreased ability to manage blood glucose has been noted in older dogs and cats.<sup>15,16</sup> Nutritional interventions for the management of glucose will be discussed by Sunvold elsewhere in this proceedings.<sup>17</sup>

### Fatty Acids

Accumulating evidence suggests that the activity of some enzymes involved with fatty acid metabolism may be altered with age. Similar to data reported in the rat,<sup>18</sup> liver delta-6 desaturase enzyme affinity decreases with age in Beagles.<sup>19</sup> Delta-6 desaturase is important in the production of gamma linolenic acid (GLA), which plays a role in modulating inflammation in the skin. Including GLA in the diet of senior dogs provides a nutrient that the older animals can no longer produce efficiently.

### Antioxidants

One of the more widely recognized theories of aging is the “Free Radical Theory of Aging” proposed by Harmon.<sup>20</sup> This theory hypothesizes that the aging process results in an accumulation of free radicals which may cause intracellular damage leading to the degenerative diseases associated with

aging (eg, arthritis, cataracts, cancer). This has led to a general interest in the ability of dietary antioxidants to protect against free radical damage in companion animals.

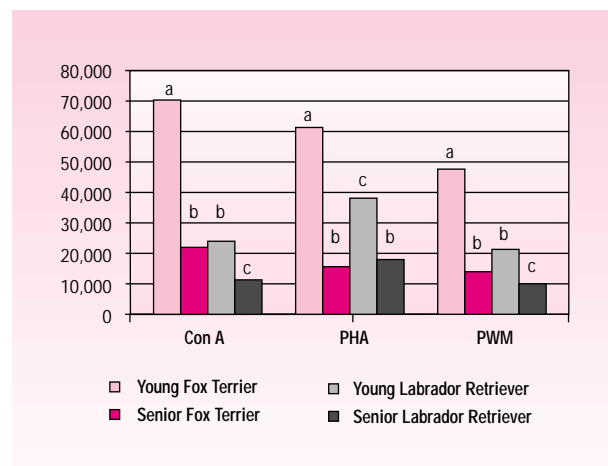
If allowed to go unchecked, free radicals can damage cell membranes, proteins, and DNA. There are a variety of ways in which free radical accumulation or oxidative stress has been measured in companion animals. This has included the measurement of TBARS or MDA for general lipid damage,<sup>21,22</sup> TAS and oxidative proteins for general oxidative status,<sup>23,24</sup> 4-HNE and isoprostanes for non-enzymatic oxidation of arachidonic acid and 8-OHdG and the comet assay for assessment of DNA damage.<sup>24-29</sup> Recent studies have demonstrated that dietary antioxidants can modulate general oxidative stress and DNA damage in dogs.<sup>24</sup>

It has been suggested that several physiological systems that change with age may respond to an antioxidant nutritional strategy. One such system is a cognitive function. It has been suggested that a decline in cognitive function is a result of aging.<sup>30</sup> This age-associated decline in cognitive function has been demonstrated in dogs as well.<sup>30-32</sup> It has been suggested that this decline may be due to oxidative stress.<sup>33</sup> Recent studies have suggested that certain antioxidants may aid in this age-associated decline in cognitive function.<sup>34</sup>

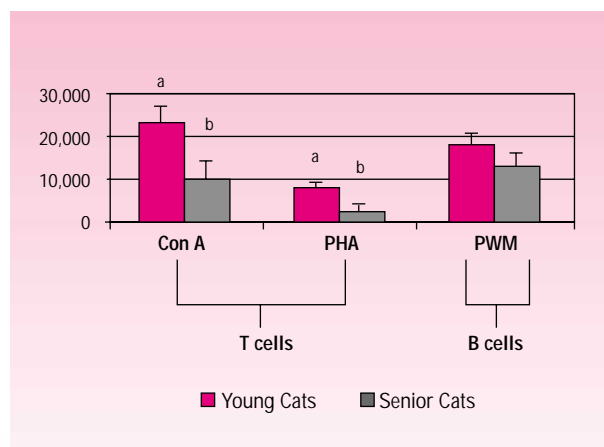
Another system that declines with age is the immune system. Similar to reports in rodents and humans,<sup>8</sup> the immune system of the dog declines with age as well. Laboratory studies have demonstrated a decline in mitogen stimulation, chemotaxis, and phagocytosis.<sup>9,35</sup> A recent longitudinal study has reported age-related changes in clinical immunological parameters such as decreased numbers of white blood cells and immature neutrophils along with increased numbers of mature neutrophils and concentrations of immunoglobulin G.<sup>36</sup>

The effect of age on immune cell activation in different breeds of dogs was examined by isolating lymphocytes from 40 young (<1.5 years old) and old (>7 years old) Fox Terriers and Labrador Retrievers. These cells were stimulated with either Concanavalin A (Con A) or phytohemagglutinin (PHA; T cell stimulants) or pokeweed mitogen (PWM; B cell stimulant). Both breeds demonstrated an age-associated decline in their ability to respond to the different mitogens (**Figure 1**). It is interesting to note that the degree of decline was greater for the Fox Terriers than the Labrador Retrievers (-216% vs -114%; -292% vs -106%; -234% vs -102% Fox Terriers vs Labrador Retrievers, Con A, PHA, and PWM, respectively).<sup>36</sup> Also, thymidine incorporation was greater in lymphocytes isolated from Fox Terriers than Labrador Retrievers. This suggests a decrease in cellular proliferative capacity in lymphocytes isolated from the larger breed. A similar age-related reduction in cellular proliferation has recently been reported in the cat (**Figure 2**).<sup>37</sup>

These data demonstrate that there is an age-related decline in immunity in dogs and cats and that this decline may increase the susceptibility of the geriatric animal to infection.<sup>36</sup> Furthermore, this rate of age-related decline may be different between breeds of dogs. The potential exists to



**Figure 1.** The effect of age and breed on T cell and B cell proliferative response in dogs. Isolated lymphocytes from young and senior Fox Terriers and Labrador Retrievers were challenged with T cell mitogens Concanavalin A (Con A) or phytohemagglutinin A (PHA) or B cell mitogen Pokeweed mitogen (PWM). Means within a mitogen treatment having different superscripts are significantly different.

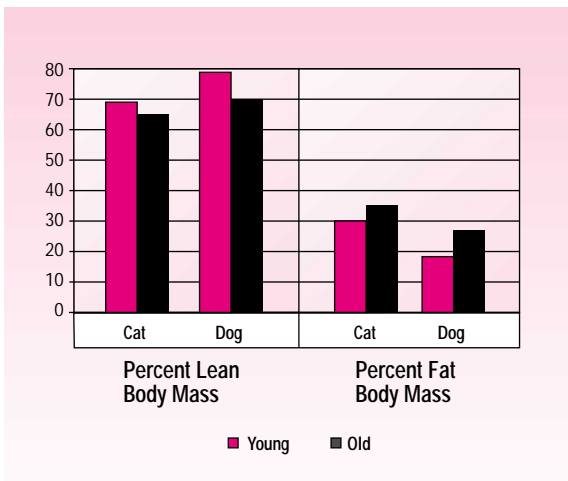


**Figure 2.** The effect of age on T and B cell proliferative response in cats. Isolated lymphocytes from young and senior cats were challenged with T cell mitogens Concanavalin A (Con A) or Phytohemagglutinin A (PHA) or B cell mitogen Pokeweed mitogen (PWM). Means within a mitogen treatment having different superscripts are significantly different.

influence this rate of decline with nutrients that enhance the canine immune response. Specifically, antioxidants such as vitamin E,  $\beta$ -carotene or lutein have been shown to have beneficial effects on the canine and feline immune system.<sup>39-41</sup> The effect of vitamin E on the aging immune system will be covered by Meydani et al.<sup>42</sup> elsewhere in these proceedings.

## Protein

Age-dependent changes in the body composition of dogs and cats are reflected in progressive reductions in lean body mass (muscle) with concurrent increases in body fat as illustrated in **Figure 3**. These alterations in body composition are similar to those observed in aging humans. It has been demonstrated in humans that muscle mass is highly



**Figure 3. Body composition in young and senior cats and dogs.** Data generated from a colony of 40 young (<1.5 year) and senior (>7 years) cats and 36 young (<1.5 year) and senior (>7 years) Fox Terriers and Labrador Retrievers. Percent lean body mass and fat body mass was determined by dual energy x-ray absorptiometry (DEXA).

vulnerable to the effects of aging based on the preferential loss of muscle mass compared with non-muscular tissues such as the liver, heart, and digestive tract.<sup>43</sup> This progressive loss of muscle throughout adult life results in skeletal muscle comprising only 27% of the body weight of elderly men as compared with 45% in young-adult males.<sup>43</sup> These losses in muscle mass are accompanied by lower rates of whole-body protein synthesis and degradation in elderly individuals.<sup>44</sup> More specifically, muscle protein turnover accounts for 30% of the whole-body protein turnover in young-adults, but decreases to 20% as individuals age due to the progressive loss of muscle mass.<sup>45</sup>

Although a number of factors are involved in the loss of lean body mass during the aging process, alterations in whole-body protein turnover are ultimately responsible for muscle wasting. Whole-body protein turnover represents the combination of protein synthesis and degradation required for the continual replacement of individual proteins located throughout the body. The loss of body protein occurs when the rate of degradation exceeds the rate of synthesis. Ideally, synthesis and degradation of body protein should be equal in order to maintain existing body protein stores.

Administering <sup>15</sup>N-glycine as a tracer amino acid<sup>46,47</sup> to young-adult (2 years of age) and geriatric (>8 years of age) Beagles showed that flux of N through the metabolic amino acid pool increased linearly as dogs consumed increasing levels of dietary protein.<sup>48</sup> Furthermore, rates of whole-body protein synthesis and degradation were 2-fold higher when these dogs consumed a diet containing 32% protein compared with those consuming diets containing 16 and 24% protein. Other researchers have also reported similar positive correlations between N flux and protein intake in adult and geriatric individuals using <sup>15</sup>N-glycine as a tracer amino acid.<sup>49,450</sup> Differences in protein turnover that are associated with increased protein consumption coincide with larger body

protein reserves in these individuals.<sup>51,52</sup> These observations were recently confirmed in young and old Fox Terriers and Labrador Retrievers.<sup>53</sup>

The loss of lean body mass that accompanies the aging process may diminish the body's ability to respond to physical trauma, infectious agents, or stress.<sup>54</sup> Decreased muscle protein reserves cannot provide sufficient quantities of amino acids that are needed for tissue repair and energy metabolism. Furthermore, the loss of lean body mass may impair the immune system and increase the susceptibility of elderly individuals to infectious organisms.<sup>55</sup> Consumption of a low-protein diet by elderly women produced negative N balance due to loss of lean body mass, which was accompanied by reduced immunocompetence.<sup>10</sup> In contrast, the consumption of a protein-adequate diet maintained N balance and lean body mass while enhancing immunocompetence in these elderly women.

Reduced protein intake resulting from decreased voluntary food consumption or the ingestion of low-protein diets by geriatric individuals may compromise their health due to the inability to maintain adequate lean body mass. As a result, protein inadequacy may accelerate the aging process due to reduced body protein reserves, suppressed immunocompetence, and decreased resistance to various infectious organisms and stress. It appears that higher levels of dietary protein are needed to provide a continual source of amino acids for tissue repair and immunocompetence. As a result, increased protein consumption should enhance the health and well-being of geriatric individuals by preserving muscle mass and delaying the effects of aging.

## CONCLUSION

The accumulation of data that define the physiology of the geriatric dog and cat demonstrate that specific nutritional formulations are warranted for the aging population companion animals. Strategies should be designed to prevent the onset of age-associated physiological changes (ie, decline in lean body mass and immune response) as well as adjust to progressive metabolic changes (ie, changes in enzyme activities for fatty acid metabolism). These nutritional formulations should take into account moderate protein levels, antioxidant vitamin adjustments, and specific fatty acids in order to address these issues. As data continue to be generated, further nutritional advances will provide guidance for optimizing formulations that will enhance the health of geriatric dogs and cats.

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# Balanced Non-Surgical Management of Osteoarthritis in the Older Dog

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## INTRODUCTION

Advances in our knowledge in canine nutrition and medicine have resulted in many dogs significantly surpassing previous life expectancies. One disease that has become more prevalent clinically due to a greater number of dogs clinically defined as “geriatric” than seen previously is osteoarthritis. Osteoarthritis (OA, syn. osteoarthrosis, degenerative joint disease, DJD) is a syndrome that affects synovial or diarthrodial joints and may manifest its presence by causing pain in association with degeneration of articular cartilage (loss of extracellular cell matrix and chondrocytes, inflammatory response of synovium, and critical changes in proteoglycan ratios within matrix and synovial fluid) and changes in periarticular soft tissues. Since typically a low-grade inflammatory process is associated with the

development and maintenance of the degenerative process of articular cartilage, the underlying subchondral bone response (eg, sclerosis), intra and periarticular response (eg, synovial hypertrophy, periarticular fibrosis), the term “osteoarthritis” describes the disease process of the diarthrodial joint better than the older term “degenerative joint disease”. Typically, OA is an insidiously progressive, degenerative condition that targets high motion synovial joints. Etiologies may include infectious (eg, septic arthritis) or non-infectious (eg, immune mediated, trauma, developmental/congenital) environment development within the joint. This discussion will be limited to the non-surgical management of secondary low-inflammatory-based OA or what has been classically labeled “secondary degenerative joint disease” or non-infectious, non-immune-mediated osteoarthritis.

Micro and macroscopic changes within the synovial joint may result in the clinical signs of lameness due to joint pain (synovitis, microfractures of subchondral bone, osteophytes, and joint effusion/distention) (**Figure 1a,b**). The clinical signs associated with OA vary from patient to patient and may range from subclinical to a severe



**Figure 1 A.** Osteoarthritis of the stifle joint secondary to chronic cranial cruciate ligament rupture (note osteophytes [O] and cartilage erosions [E]).

functional disability. Fundamentally, no one treatment will be all encompassing for all patients with OA. A treatment “pyramid” with three major components — weight control, exercise modification, and pharmaceuticals/non-pharmaceuticals — must be considered when non-surgically managing a patient with OA (**Figure 2**). Exclusion of one or more of these components from a treatment protocol will result in an overall poorer clinical response from the patient.

## WEIGHT CONTROL

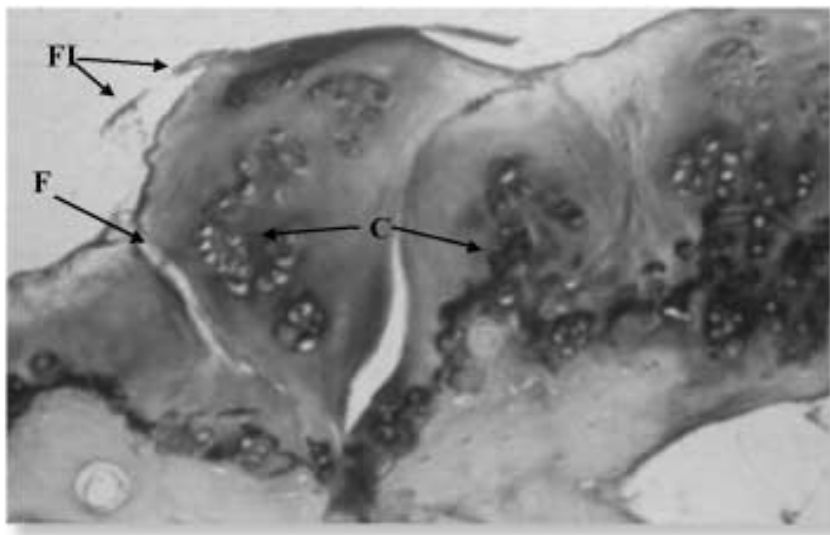
Obesity is a major risk factor for the development of OA<sup>1,2</sup> while weight loss can reduce the symptomatic effects of OA in humans.<sup>3,4</sup> Until recently, it was assumed that the same held true in other animals. A recent clinical study investigating the effects of obesity on dogs with hip dysplasia concluded that overweight dogs that achieved an 11–18% body weight reduction were significantly less lame compared to their pre-weight reduction lameness scores.<sup>5</sup> Currently, Washington State University is performing a study to examine the effects of obesity on the clinical expression of OA in dogs with canine hip dysplasia.

Weight control can be one of the most challenging aspects of the medical management of OA in dogs for several reasons.

1. A patient that is clinically inhibited by moving an OA joint(s) will not be able to utilize consumed or stored body energy efficiently and will instead increase body stores of energy (fat) when given a constant caloric intake.
2. Dogs with underlying endocrine disease (eg, hyperadrenocorticism, hypothyroidism) will have the metabolic propensity to maintain body fat stores even in the face of a reducing diet.
3. Dogs that are in a multi-pet household (eg, other dogs and cats) are more prone to consume greater volumes of food than dogs in single-pet households.
4. An inaccurate estimation of animal’s ideal body weight.
5. An inaccurate estimation of animal’s energy requirements.
6. The owner’s lack of willingness to be proactive in trying to reduce their pet’s body weight.

Any one or a combination of the above factors will maintain the obese patient indefinitely.

Prior to starting a weight-reducing program, a complete physical exam should be performed. The clinical history (attempted weight reduction in the past with poor results, lethargy, “heat seeking,” PU/PD, etc.) and physical exam findings (pendulous abdomen, symmetrical alopecia, recurrent dermatopathy, etc.) may warrant a complete



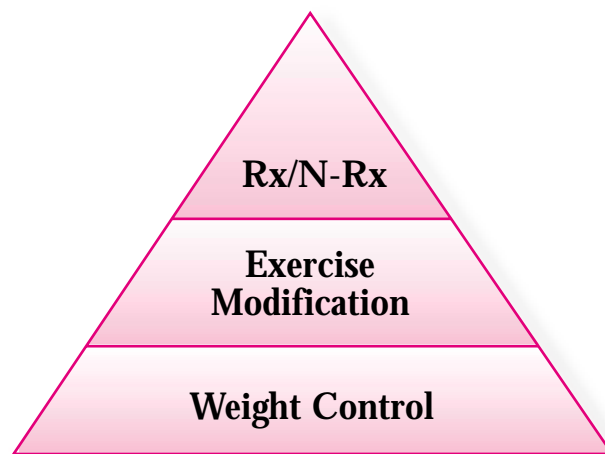
**Figure 1 B.** Photomicrograph of degenerative articular cartilage (10X) (note fibrillation [FI], fissures [F], cloning nests of chondrocytes [C]). Photomicrograph courtesy of Dr. S.P. Arnoczky.

minimum database (CBC, serum chemistry profile, UA) to rule out metabolic disease or endocrinopathies.

Weight reduction can be obtained in healthy patients by three methods:

1. Reducing current caloric intakes; using reductions by 33 to 50% of the “normal” volume of the regular diet.
2. Calculating caloric content of regular diet and caloric needs based on basal metabolic rates.
3. Use a specially formulated commercial diet with recommended intake volumes per the manufacturer.

Avoiding additional calories in the form of table scraps or “dog treats” is also usually necessary to achieve weight loss in a dog. The frequency of feeding must also be considered during weight reduction. Dogs on weight reducing plans appear to be less hungry if fed a divided volume of the reducing diet over the course of the day. Feeding inbetween “snacks” of low-calorie and high-fiber quality (raw carrot



**Figure 2.** Osteoarthritis treatment pyramid.

sticks, raw celery sticks, non-flavored rice cakes) or ice cubes will satisfy most dogs. Appropriate caloric restriction should result in the loss of 1–2% of body weight per week.<sup>6</sup>

All weight reduction/control programs must include an exercise program to ensure constant weight loss and eventual body weight maintenance. To encourage activity in the debilitated OA patient, regular pharmacologic treatment may be required for a short period until the patient becomes more ambulatory.

## MODIFICATION OF EXERCISE AND ACTIVITY

It is known from the human literature that exercise is very important in maintaining strength, stamina, joint range of motion, and less dependency on medication when OA patients are allowed to exercise.<sup>7–11</sup> It is assumed that the same is true in other animals as well and supported by a recent study in hamsters.<sup>12</sup> Therefore, an important aspect in the management of OA in animals should be a controlled exercise. Depending on the animal's activity history, it may be necessary to modify a patient's regular level and type of activity that is part of that animal's daily exercise regime.

It may be intuitive that an OA animal should not be allowed to have hard impact, prolonged exercise activity, but controlled clinical studies have not been performed to evaluate this recommendation. However, from clinical experience, practitioners are used to hearing the usual owner's report of greater clinical signs in OA patients after hard, prolonged activity. It is known from kinetic and kinematic gait analysis that dogs with OA will modify their gait to reduce the load of weight-bearing and motion of the affected joint.<sup>13–15</sup> It is therefore safe to assume that prolonged "over activity" should result in greater modification of gait due to exacerbation of the discomfort associated with an OA joint. Some recommendations for the duration of certain activities in dogs have been made,<sup>16</sup> but recommendations for activity duration can also be based on "common sense" and the observations made by the owner of their pet's apparent gait response/comfort level to an activity period.

Just as important as duration of activity is the type of activity involved with the animal's daily life style. Low-impact activities (eg, walking, cycling) have positive effects on human OA patients.<sup>7,8,17</sup> In veterinary medicine, low-impact activities (walking, swimming) have been traditionally favored over hard-impact aerobic activities (jumping, hard starting/running, vigorous climbing/running on irregular terrain), which can overstress degenerative joints. High-impact activities may overstress OA joints and increase the inflammatory condition of OA. Low-impact activities are thought to reduce loads on an OA joint and result in less discomfort for the patient in maintaining good muscle strength/mass and

joint function. Walking under controlled conditions (leash restraint) and/or swimming (**Figure 3**) can be recommended to the owner with further instructions to eventually attempt to have the patient increase the duration of these activities gradually so long as the animal appears to remain comfortable in doing so.

## PHARMACOLOGIC/NONPHARMACOLOGIC OSTEOARTHRITIS AGENTS

The primary goal with the pharmacologic management of OA is to relieve the patient of discomfort associated with joint movement. Ideally, this would involve oral or injectable agents with analgesic, antiinflammatory, and potential chondromodulating properties (disease-modifying OA agents, aka "DMOA"). Such agents would ideally biochemically block the inducible cyclooxygenase-2 (COX-2) and lipoxygenase pathways. Nonsteroidal antiinflammatory drugs (NSAID) have been developed for this purpose (**Table 1**) but generally, do not all selectively block mainly the COX-2 pathway<sup>18–20</sup> or leukotrienes production from the lipoxygenase pathway.<sup>21–23</sup>

Two NSAIDs (carprofen, etodolac) have been recently approved for use in dogs. These NSAIDs are considered to have a low COX-2:COX-1 ratio, but have toxicity potential as with any NSAID. Concerns are present with long-term, chronic therapy with NSAIDs. Hepatic toxicosis due to NSAID administration has been reported<sup>24</sup>; however, all NSAIDs have a toxicity potential especially if a patient has underlying hepatic or renal disease, or a thrombocytopeny. Several in vivo studies using chondrocyte cell cultures or cartilage explants have reported a decrease in proteoglycan synthesis in those tissues incubated with selected NSAIDs.<sup>25–28</sup> It would appear to be a wiser clinical practice to administer NSAIDs on a PRN basis especially for the patient that has only intermittent discomfort due to osteoarthritis.



**Figure 3.** Swimming physical therapy.

**Table 1. Selected nonsteroidal antiinflammatory drug doses for the dog.**

Drug	Dose	Route	Strength	Side Effects
carprofen (Rimadyl)	2.2 mg/kg q 12hr	PO (inj. soon)	25, 50, 75, 100 mg tablets	vomiting, diarrhea, changes in appetite, appetite, lethargy, behavioral changes, constipation
etodolac (Etogesic)	10–15 mg/kg q 24hr	PO	150, 300 mg tablets	vomiting, lethargy, diarrhea/loose stool, hypoproteinemia, behavior change, urticaria, anorexia, regurgitation
*ketoprofen (Orudis)	1–2 mg/kg loading (once) 1 mg/kg q 24 hr (maint.) 1 mg/kg q q 24 hr	PO  SC	12.5 mg tablets (OT)  Injectable	vomiting, diarrhea, serum increase of creatinine
*meloxicam (Metacam; approved in Europe and Canada)	.1–.2 mg/kg q 24 hr	PO, SC	Suspension Injectable	vomiting
*piroxicam	0.3 mg/kg q 24hr or once, e.o.d	PO	10, 20 mg capsules	vomiting
*rofecoxib (Vioxx™)	5 mg/kg	PO	12.5, 25, 50 mg tablets Suspension	vomiting
*aspirin (Ascriptin)	10–20 mg/kg q 8-12 hr	PO	325 mg (w/ Malox) (OT)	vomiting, lethargy, gastroduodenal ulceration
* currently not labeled for small animal use in the United States OT = “Over-the-Counter”				

Disease-modifying osteoarthritis agents (DMOA) have recently been developed for the treatment of human and veterinary OA patients. These agents have become commonplace in the treatment of OA despite the lack of definitive scientific studies confirming their efficacy. Most of these products contain mixtures of glucosamine and chondroitin sulfate, which supposedly enhance cartilage health by providing the necessary precursors to maintain and repair cartilage. Glucosamine and chondroitin sulfate reportedly have a positive effect on cartilage matrix, enhance proteoglycan production, and inhibit catabolic enzyme production or activity in OA joints. These properties have contributed to the labeling of these agents as “chondroprotective”.<sup>29</sup> With the exception of one product, which is a true pharmaceutical by definition (Adequan®, Luitpold Pharmaceuticals, FDA approved in horses and dogs), these agents are marketed as oral nutritional supplements and not “drugs” and as such, the Federal Drug Administration does not require the manufacturer to provide efficacy data of their product. Bioavailability reported of orally-ingested forms of glucosamine and chondroitin sulfate are 87%<sup>30,31</sup> and 70%<sup>32</sup> in humans and experimental animals, respectively. Limited

investigations have been performed on the in vitro and in vivo activity of glucosamine and chondroitin sulfate separately, but products containing both agents have become popular for treating OA symptoms in humans and other animals. Synergism with glucosamine and chondroitin sulfate has recently been demonstrated histologically and with in vivo biochemical analysis in a rabbit OA model.<sup>33</sup>

Two commonly used combination glucosamine and chondroitin sulfate oral products in dogs are Cosequin® (Nutramax) and Glycoflex® (Vetri-Science Laboratories). Although clinically noted not to have predicable efficacy in all dogs, this combination of glycosaminoglycans appears to have a prophylactic effect on the development of OA in dogs. Dogs undergoing a Pond-Nuki model for the development of OA with or without stifle stabilization that were administered Cosequin® for 5 months following surgery subjectively had less OA and less periarticular fibrosis than dogs not receiving Cosequin®.<sup>34</sup> Chymopapain-induced acute carpal synovitis was significantly attenuated based on nuclear scintigraphy and lameness evaluation when dogs were pre-treated with glucosamine and chondroitin sulfate (Cosequin®).<sup>35</sup> Current research suggests that glucosamine and chondroitin sulfate

products may have been prophylactically beneficial in patients that are prone to develop OA (eg, CHD, elbow dysplasia, OCD, cranial cruciate ligament injury, etc.) or patients that may aggravate preexisting OA with activity. Further controlled clinical studies are still truly warranted to support these statements.

Injectable forms of DMOA available are Adequan<sup>®</sup>, which is a polysulfated glycosaminoglycans (PSGAG) product, and hyaluronic acid, a nonsulfated glycosaminoglycan (GAG). The U.S. product (Adequan<sup>®</sup>) and European product (Arteparon<sup>®</sup>) have been used in horses and dogs. Though conflicting evidence exists that PSGAGs have a positive anabolic effect on hyaline cartilage, studies have shown that PSGAG may decrease hyaline cartilage catabolism. In one study, immature dogs prone to hip dysplasia that were administered Adequan<sup>®</sup> developed better hip conformation than dogs that were not treated with Adequan<sup>®</sup>.<sup>36</sup> Coxofemoral joint assessment made post euthanasia was not significantly different from untreated dogs.<sup>36</sup> A clinical study investigating the use of PSGAG on hip dysplasia patients found no significant difference in orthopedic scores (lameness, range of motion, pain on manipulation of hip joints) compared to PSGAG nontreated dogs.<sup>37</sup> In a meniscectomy model in dogs, PSGAG provided partial protection to articular cartilage damage associated with the meniscectomy.<sup>38</sup> Polysulfated glycosaminoglycans have been reported to have chondroprotective properties in joints with a chemically-induced articular cartilage damage model vs. no effect on a physical articular cartilage damage model in horses.<sup>39</sup> Recently, there have been anecdotal reports indicating that there may be a positive synergism between injectable PSGAG and oral glucosamine and chondroitin sulfate when administered concurrently to a patient.

Hyaluronic acid (sodium hyaluronate, HA) is a major component of synovial fluid. Hyaluronic acid is postulated to enhance joint health by increasing the viscosity of the joint fluid and by reducing inflammation and scavenging free radicals. A study using a Pond-Nuki model for OA in dogs followed by intraarticular injections of HA did not modify OA and reduced overall proteoglycan concentrations in treated stifles.<sup>40</sup>

Other products reported that have disease-modifying, anti-OA potential include pentosan polysulfate, tetracyclines (doxycycline, minocycline, and modifications of these molecules), S-adenosyl-L-methionine (SAMe), methylsulfonylmethane (MSM), capsaicin, and fatty acid ratio manipulation (omega-6:omega-3). To date, the limited number of studies conducted suggest that some of these products may eventually have a place as adjuncts to the treatment of OA in animals.<sup>41-49</sup>

Adjuncts to pharmacologic, exercise/activity, and weight control treatment that can also be considered are the application of heat, cold, massage, hydrotherapy, ultrasound/diathermy, and electrotherapy.<sup>16</sup> Although based on anecdotal observations only, these adjuncts appear to help some patients. Well-controlled clinical trials are needed to test the

supposition that these modalities are as positively effective in veterinary OA patients as they are in human OA patients.

## SUMMARY

Geriatric dogs can be significantly affected by osteoarthritis; however, new concepts in a balanced management of OA can result in an acceptable quality of life for the OA patient. Non-surgical management must be considered beyond conventional and non-conventional pharmacologic treatment to include a balance created between exercise/activity and weight control management. Failure to consider this treatment “pyramid” concept will usually result in a poorer clinical response to therapy and quality of life as perceived by the owner of the OA patient. Excellent progress continues in the development of new pharmacologies and other agents to combat or even reverse the degenerative processes of OA. In contrast, research and development into exercise/activity management for the OA companion animal lags significantly behind that of human medicine, but since the mid-1990’s, is beginning to grow in interest in veterinary medicine. Nonetheless, large controlled clinical trials are needed for “evidence-based” treatment protocols (controlled clinical trials) that will allow us to treat our OA patients beyond the “clinical experience”.

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# Early Detection and Management of Canine Renal Disease

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## INTRODUCTION

Renal disease leading to chronic renal failure (CRF) is a major cause of morbidity and mortality in dogs. Nephron damage associated with chronic renal disease is usually irreversible and progressive. Whether the underlying disease process primarily affects glomeruli, tubules, interstitial tissue, or the blood supply to the nephron, irreversible damage to any of these components renders the entire nephron nonfunctional. Healing of irreversibly damaged nephrons occurs by replacement fibrosis and therefore a specific etiology is often difficult to determine. Due to the large functional renal reserve and the compensatory hypertrophy of remaining nephrons, clinical signs and laboratory data compatible with CRF are usually not present until >75–85% of all nephrons are nonfunctional. At this point, improvement of renal function is usually not possible and therefore management of the canine CRF patient is aimed at reducing “renal workload” as well as the clinical signs associated with the decreased renal function. Early detection of canine renal disease, prior to the onset of CRF, should improve our ability to manage these patients.

## ETIOLOGY

The cause of CRF is usually difficult to determine. Due to the interdependence of the vascular and tubular components of the nephron, the end point of irreversible damage to any portion of the nephron is the same. Morphologic heterogeneity between nephrons exists in the chronically diseased kidney with the spectrum of changes ranging from severe atrophy to marked hypertrophy. The histologic changes are not process specific and, therefore, an etiologic diagnosis is frequently not possible.

Until relatively recently, canine glomerular disease was thought to be uncommon and unimportant. It is now recognized that glomerulonephritis (GN) in dogs is relatively common and can lead to chronic renal insufficiency/failure. For example, in a study of 76 dogs with chronic renal disease, 40 (52%) had glomerular disease rather than nonglomerular disease.<sup>1</sup> In another study of dogs with chronic renal disease that received renal allografts, GN was the underlying renal disease in 7 of 15 cases.<sup>2</sup> Interestingly, a urine protein/creatinine ratio < 5 was required for inclusion in this study to help exclude GN that might affect the allograft.<sup>2</sup> Even though the inclusion criteria were biased against GN, 47% of the dogs studied had GN. The magnitude of this problem is emphasized by additional studies that have shown the incidence of GN in dogs to be as high as 43–90%.<sup>3,4</sup>

*Early detection of canine renal disease, prior to the onset of CRF, should improve our ability to manage these patients.*

## CLINICAL SIGNS AND LABORATORY DATA

Clinical signs of CRF are nonspecific and include lethargy, anorexia, vomiting, dehydration, and emaciation. A diagnosis of renal failure is confirmed when persistent azotemia with concurrent isosthenuria or minimally concentrated urine is documented. Clinical signs associated with CRF are often relatively mild for the magnitude of the azotemia in comparison with acute renal failure. Dogs with CRF often have a history of weight loss and polydipsia-polyuria and clinicopathologic findings of a nonregenerative anemia and small and irregular kidneys.

In dogs with glomerular disease, loss of plasma proteins into the urine is one of the earliest functional defects. Clinical signs associated with mild to moderate proteinuria, however, are often lacking. Consequences of severe plasma protein loss may include sodium retention, hypercoagulability, muscle wasting, and weight loss. Persistent proteinuria greater than 3.5 g/day will often result in the nephrotic syndrome. The combination of significant proteinuria, hypoalbuminemia, ascites or edema, and hypercholesterolemia is defined as the nephrotic syndrome. In addition to these clinicopathologic

findings, hypertension and hypercoagulability are frequent complications in dogs with nephrotic syndrome.

There does not appear to be a relationship between proteinuria and glomerular filtration rate in dogs with GN.<sup>5</sup> Azotemia and renal insufficiency/failure occur as more and more nephrons are irreversibly damaged and become nonfunctional. Late in the disease process, proteinuria tends to diminish associated with the decreased number of affected glomeruli. Plasma protein loss on an individual remaining nephron basis, however, may remain abnormally high. Indeed, individual nephron hyperfiltration and proteinuria have been documented in dogs with the remnant kidney model of CRF.<sup>6</sup>

## EARLY DETECTION OF RENAL DISEASE

Most canine CRF occurs in middle to older aged dogs. An annual health examination, that includes a complete blood count, serum biochemistry profile, and urinalysis, is one of the best ways to detect declining renal function (**Table**). Special attention should be paid to decreases in appetite, body weight, packed cell volume, and urine specific gravity. Conversely, increases in serum urea nitrogen, creatinine, and phosphorus, or urinary excretion of protein may signal the onset of renal disease. Plotting the inverse of the serum creatinine concentration versus time can demonstrate a decrease in renal excretory function. Dogs may

**Table.** Clinicopathologic findings that may be associated with early renal disease in dogs

Annual Health Examinations
<b>Decreases in:</b>
Appetite
Body weight
Packed cell volume
Urine specific gravity
<b>Increases in:</b>
Serum urea nitrogen concentration
Serum creatinine concentration
Serum phosphorus concentration
Proteinuria
Bacteriuria

also become more susceptible to bacterial urinary tract infections as their ability to concentrate urine decreases and the antibacterial properties of their urine decrease. If any of the above parameters suggest the possibility of renal disease, an ultrasound examination should be used to evaluate kidney tissue architecture. Pyelonephritis, renoliths, and renal cortical fibrosis can be demonstrated by ultrasound. Percutaneous or ultrasound-guided renal biopsy can be utilized to confirm or further define renal cortical disease.

## IMPORTANCE OF PROTEINURIA

There is increasing evidence in laboratory animals and human beings that proteinuria can cause glomerular and tubular damage and result in progressive nephron loss. Proteinuria can occur secondary to immune-mediated glomerular damage or as a consequence of the nephron hypertrophy and glomerular hyperfiltration that results with nephron loss. Plasma proteins that have crossed the glomerular capillary wall can accumulate within the glomerular tuft and stimulate mesangial cell proliferation and increased production of mesangial matrix in human beings.<sup>7</sup> In addition, excessive amounts of protein in the glomerular filtrate can be toxic to human tubular epithelial cells and can lead to interstitial inflammation, fibrosis, and cell death.<sup>8</sup> Proximal tubular cells normally reabsorb protein from the glomerular filtrate by endocytosis. Albumin and other proteins accumulate in tubular cell lysosomes and are then degraded into amino acids and returned to the circulation. In proteinuric conditions, excessive lysosomal processing can result in swelling and rupture of lysosomes causing enzymatic damage to the cytoplasm in rat kidneys.<sup>9</sup>

**An annual health examination, that includes a complete blood count, serum biochemistry profile, and urinalysis, is one of the best ways to detect declining renal function.**

Several studies in human patients with proteinuric renal disease suggest that proteinuria is linked to renal disease progression. In a 5-year study of 176 patients with non-insulin dependent diabetes mellitus, baseline albuminuria was a predictor for the development of incipient nephropathy.<sup>10</sup> Similarly, in people with insulin-dependent diabetes mellitus and established diabetic nephropathy, higher levels of proteinuria at baseline predicted progression of the nephropathy over a median period of 3 years.<sup>11</sup> In another study of people with chronic GN, the decrease in proteinuria associated with several different treatments predicted the change in the slope of the reciprocal of the serum creatinine over 6 months.<sup>12</sup> Paired renal biopsies taken 5.8 years apart in people with insulin-dependent diabetes mellitus showed that mesangial expansion was linked to microalbuminuria and that tubulointerstitial changes occurred as a result of advanced glomerular injury.<sup>13</sup> In a 3-year study of 583 human beings with various renal diseases, the angiotensin converting enzyme (ACE) inhibitor benazepril reduced proteinuria and systemic blood pressure and slowed the decline in glomerular filtration rate (GFR) when compared with placebo treatment.<sup>14</sup> The protective effect of benazepril on renal function was greatest in those patients with substantial proteinuria (>3 g/24 hours) even after adjustments were made for changes in diastolic blood pressure or urinary protein loss

over time.<sup>14</sup> Finally, in a study of 7,728 nondiabetic people, macroalbuminuria was independently associated with decreased GFR.<sup>15</sup>

Evidence linking proteinuria to progression of renal disease in dogs is less convincing. As stated earlier, individual nephron hyperfiltration and proteinuria have been documented in dogs with the remnant kidney model of renal failure.<sup>6</sup> However, treatments that have slowed the functional decline and/or histologic changes associated with this model have had variable effects on proteinuria. Angiotensin converting enzyme inhibition and omega-3 fatty acid supplementation have decreased proteinuria and slowed progression,<sup>16,17</sup> however, calcium blockade treatment resulted in increased mesangial cell proliferation despite decreasing proteinuria.<sup>16</sup> Other treatments, such as reduction of dietary phosphorus, decreased renal disease progression in remnant kidney dogs but had no effect on proteinuria.<sup>18</sup> In dogs with experimentally induced immune complex GN, treatment with a thromboxane synthetase inhibitor decreased proteinuria and attenuated the development of glomerular lesions but had no effect on established lesions.<sup>19,20</sup> More recently, reduction of proteinuria via ACE inhibition (enalapril) was associated with slowed progression of renal disease in dogs with two different types of naturally-occurring glomerulopathies.<sup>21,22</sup>

## TREATMENT OF PROTEINURIA

Most canine glomerular disease is thought to be associated with the presence of immune complexes in glomerular capillary walls. Generation of these immune complexes is dependent on the presence of antigen and therefore the most important treatment for glomerular disease is identification and correction of any underlying disease processes. However, since an antigen source or underlying disease process is often not identified or is impossible to eliminate (eg, neoplasia), other treatments are often necessary. Immunosuppressive drugs have been employed in the treatment of canine GN, however, their efficacy is usually minimal. If immunosuppressive drugs are employed, proteinuria should be quantitated frequently to assess the effects of treatment. In some instances, immunosuppressive treatment may exacerbate glomerular lesions and proteinuria.

One of the treatments that is showing promise in the management of proteinuric renal disease in the dog is ACE inhibition. As mentioned earlier, treatment with enalapril improves renal function and prolongs survival in male Samoyed dogs with hereditary nephritis.<sup>21</sup> This primary glomerular disease results in chronic renal failure in affected dogs prior to one year of age. In another study in dogs with unilateral nephrectomies and experimentally-induced diabetes mellitus, ACE inhibition (lisinopril) reduced glomerular transcapillary hydraulic pressure and glomerular cell hypertrophy as well as proteinuria.<sup>16</sup> In dogs with naturally-occurring GN, treatment with enalapril reduced proteinuria and systolic blood pressure and prevented an

increase in serum creatinine concentrations when compared to placebo-treated dogs.<sup>22</sup> Finally, although not directly applicable to dogs, it is interesting to note that benazepril sustained single nephron GFR, reduced systemic blood pressure, and increased whole kidney GFR in cats with remnant kidney CRF.<sup>23</sup>

Angiotensin converting enzyme inhibition probably decreases proteinuria and preserves renal function associated with glomerular disease by a combination of mechanisms. In dogs, administration of lisinopril decreases efferent glomerular arteriolar resistance which results in decreased glomerular transcapillary hydraulic pressure and decreased proteinuria.<sup>16</sup> In rats, administration of enalapril prevents the loss of glomerular heparan sulfate that can occur with glomerular disease.<sup>24</sup> Heparin sulfate contributes to the negative charge of the glomerular capillary wall. This negative charge tends to repel other negatively charged proteins such as albumin and therefore decreases the filtration of albumin. Angiotensin converting enzyme inhibitors are also

thought to attenuate proteinuria by decreasing the size of glomerular capillary endothelial cell pores in people.<sup>25</sup> In addition, the antiproteinuric and renal protective effects of ACE inhibitors may be associated with improved lipoprotein metabolism. Lipid deposition in the glomerular mesangium can contribute to proteinuria and glomerulosclerosis. In human beings with nephrotic range proteinuria, ACE inhibition not only decreases proteinuria but also reduces plasma concentrations of low density lipoprotein-cholesterol and triglycerides.<sup>26</sup> Administration of lisinopril in dogs can also slow glomerular mesangial cell growth and proliferation that can alter the permeability of the glomerular capillary wall and lead to glomerulosclerosis.<sup>16</sup> Finally, ACE inhibitors are nonspecific enzyme inhibitors and in addition to blocking the conversion of angiotensin I to angiotensin II, they also inhibit the degradation of bradykinin by blocking kininase II. Bradykinin is a vasodilatory hormone that selectively dilates efferent glomerular arterioles and enhances the formation of nitric oxide and prostacyclin. Accumulation of bradykinin is thought to have beneficial renal effects in rats and dogs.<sup>27,28</sup>

In addition to the above considerations, supportive therapy is also important in the management of proteinuric renal disease. This supportive care should be aimed at decreasing hypertension, edema, and the tendency for thromboembolism to occur. Sodium reduced diets (<0.3% dry matter) are often recommended and vasodilators and diuretics may be used as necessary. Reduction of systemic hypertension may reduce intraglomerular hypertension, especially in dogs with renal disease that has resulted in loss of autoregulation of renal blood flow. Measurement of

**Supportive therapy is also important in the management of proteinuric renal disease.**

antithrombin III and fibrinogen concentrations may be helpful in determining which patients should be treated with anticoagulant therapy. Dogs with antithrombin III concentrations less than 70% of normal and fibrinogen concentrations greater than 300 mg/dL are candidates for therapy. Aspirin and coumadins have been employed for anticoagulant therapy; however, low-dose aspirin is easily administered on an outpatient basis and does not require extensive monitoring, as does coumadin treatment. Since fibrin accumulation within the glomerulus is a frequent consequence of glomerulonephritis, anticoagulant treatment may serve a dual purpose. Finally, reduced-quantity, high-quality protein diets should also be recommended in an attempt to decrease glomerular hyperfiltration and proteinuria.

## SUMMARY

Proteinuria can indicate the presence of glomerular disease prior to the onset of azotemia. Although a direct pathogenetic link between glomerular disease, proteinuria, and progressive renal damage has not been established in the dog, attenuation of proteinuria has been associated with attenuation of renal functional decline in several canine studies. We need to continue to increase our understanding of the effects of proteinuria on the glomerulus, the tubule, and the interstitium in the dog. It is quite possible that proteinuria is more than just a diagnostic marker of glomerular disease.

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# Vitamin E, Immunity, and Aging

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## INTRODUCTION

Vitamin E is composed of a group of chemically related compounds called *tocopherols* and *tocotrienols*.  $\alpha$ -Tocopherol is considered to be the most important tocopherol since it has been reported to be the most physiologically active and it constitutes 90% of the tocopherols in human and animal tissues.<sup>1</sup> Since  $\alpha$ -tocopherol is the most active form of vitamin E, it is the compound most often supplemented in commercially prepared pet and human foods. Within the body, vitamin E is found in small concentrations in almost all tissues, although the liver possesses the ability to store large quantities.

Vitamin E is synthesized by a variety of plants in nature. Food sources that are rich in vitamin E (tocopherols) include wheat germ and corn, cottonseed, soybean, and sunflower oils. The amount of vitamin E contained in oil is directly proportional to the concentration of linoleic acid in that oil. Another potential source of vitamin E is egg yolks; however, the amount of vitamin E in the yolk depends on the diet of the hen. Due to its oxidant-antioxidant properties, commercially prepared food sources rich in vitamin E are susceptible to oxidation and degradation along with the fat

in the food. Therefore proper storage of the foods is critical in order to provide the necessary amount of vitamin E and to prevent degradation.

Vitamin E has a fundamental role in cellular metabolism. Vitamin E functions to protect cells and cellular membranes against the potentially damaging effects of reactive oxygen species, which are formed during normal metabolism as well as those that are encountered in the environment. In addition, vitamin E has been shown to have other biological effects (eg, regulation of signal transduction) which are independent of its antioxidant effects.<sup>2</sup> Therefore, vitamin E is an essential nutrient for combating a variety of oxidative stresses including immunological stress.

## VITAMIN E AND IMMUNITY

The influence of nutrition on the immune response has been widely investigated over the years. Deficiencies in many macronutrients and micronutrients have long been suspected to have a negative impact on various physiological processes including various functions of the immune system. Deficiencies in macro- and micronutrients have been linked with the inability of a host to mount an appropriate immune response. More recent research has documented that supplementation above accepted requirements may positively affect the immune system. Vitamin E supplementation has undergone extensive testing and scrutiny in this regard.

The oxidant-antioxidant balance is an important determinant of immune cell function not only to maintain the integrity and functionality of membrane lipids, cellular proteins, and nucleic acids, but also to control signal transduction and gene expression in immune cells. The cells of the immune system are particularly vulnerable to changes in the oxidant-antioxidant balance because of the relatively high concentration of polyunsaturated fatty acids in their plasma membranes. These cells are also frequently exposed to changes in this balance because high levels of reactive oxygen intermediates are produced as byproducts of their normal function.

Vitamin E is one of the most powerful biological antioxidants; its main function is to protect cellular lipids against oxidation. Therefore, it is not surprising that (1) the cells of the immune system have higher concentrations of vitamin E compared with other cells<sup>3,4</sup> and (2) severe or marginal deficiency of vitamin E adversely affects the immune system in animals and humans<sup>3</sup> (**Table 1**). It should be noted that the influence of supplemental vitamin E on immunity has been reported in various species<sup>6</sup> (**Table 2**). One unique feature of vitamin E is that supplementation with higher than

**Vitamin E is an essential nutrient for combating a variety of oxidative stresses including immunological stress.**

Table 1. Vitamin E deficiency and the immune response

Species	Immune Response Index	Effect	Reference
<b>Rodents</b>	T cell mitogenesis	Decreased	24
	T helper cell function	Decreased	24
	B cell mitogenesis	Decreased	24
	Plaque-forming cells	Decreased	25
	Antibody titer	Decreased	25
	Macrophage Ia expression	Decreased	26
	Macrophage phagocytosis	Decreased	27
	Macrophage lipid hydroperoxide production	Increased	27
	Polymorphonucleocyte chemotaxis	Decreased	27
	Polymorphonucleocyte phagocytosis	Decreased	28
	Polymorphonucleocyte hydrogen peroxide production	Increased	27
<b>Pigs</b>	T cell mitogenesis	Decreased	29
<b>Lambs</b>	T cell mitogenesis	Decreased	30
<b>Dogs</b>	T cell mitogenesis	Decreased	31
<b>Chickens</b>	Antibody titer against sheep red blood cells	Decreased	15
<b>Humans</b>	T cell mitogenesis	Decreased	32
	Interleukin-2 production	Decreased	32
	Delayed-type hypersensitivity	Decreased	32
	Polymorphonucleocyte phagocytosis	Decreased	33
	Polymorphonucleocyte chemotaxis	Decreased	33

the recommended dietary allowance has been demonstrated to enhance cell-mediated and humoral immune responses and resistance to infections. In addition, vitamin E supplementation above the recommended dietary allowance has been shown to be safe and non-toxic in several safety studies.<sup>1</sup> Thus, researchers have been interested in examining the role of antioxidants, in particular vitamin E, in maintaining an optimal immune system in the aged.

## AGING AND IMMUNITY

Senior dogs and cats are a growing segment of our companion animal population. According to a 1991 survey, there were approximately 13.6 million dogs and cats over the age of 11. This comprises a large percentage of the pet population and an ever-increasing percentage of the animals brought to veterinary clinics. The majority of veterinarians agree that senior pets can benefit from specialized care and nutrition. Therefore, it is of primary importance that we understand how nutrition (antioxidants) affects the immune system and whether or not we can use nutrition (antioxidants) as a modality to combat age-associated diseases.

Aging is associated with a dysregulation of the immune system,<sup>7</sup> which contributes to an increased incidence of diseases, infections, and tumors. Although many cells of the immune system (ie, stem cells, macrophages, and B cells)

show age-related dysregulation, the most pronounced alterations occur in T cells.<sup>7,8</sup> This dysregulation of T cells leads to an increased susceptibility to viral and intracellular pathogens as well as tumors and neoplastic diseases. Dysregulated T cell-mediated immunity is demonstrated in vivo by decreased antibody production (mediated via B cells) and the inability of aged humans and laboratory animals to develop an appropriate delayed-type hypersensitivity skin response (DTH). The decrease in specific antibody production has been observed for both primary and secondary antibody responses. Among in vitro measures of T cell function, the ability of T cells to proliferate in response to antigens or the polyclonal T cell mitogens (eg, Concanavalin A [Con A] or phytohemagglutinin [PHA]) and their production of interleukin-2 (IL-2) has been shown to consistently decrease with age.<sup>7</sup> An age-associated increase in prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and its contribution to the reduction of antibody production, DTH, IL-2 production, and lymphocyte proliferation have also been reported.<sup>9-11</sup>

## VITAMIN E MODULATION OF IMMUNITY IN THE AGED

An optimal level of vitamin E is needed in all age groups for maintenance of the immune response. This need, however, seems to be more critical in aged humans and

Table 2. Vitamin E supplementation and the immune response

Species	Immune Response Index	Effect	Reference
Rodents	T cell mitogenesis	Increased	34
	T helper cell function	Increased	35
	B cell mitogenesis	Increased	34
	Antibody titer	Increased	15
	Plaque-forming cells	Increased	34
	Interleukin-2 production	Increased	13
	Delayed-type hypersensitivity	Increased	13
	Natural killer cell activity	Increased	36
	Prostaglandin E <sub>2</sub> production	Decreased	13
Chickens	Antibody titer	Increased	37
	Plaque-forming cells	Increased	15
Pigs	Lymphocyte proliferation	Increased	38
Calves	Lymphocyte proliferation	Increased	20
Sheep	Antibody titer	Increased	39
Humans	Polymorphonuclear cell phagocytosis	Increased	40
	Polymorphonuclear cell chemoluminescence	Decreased	40
	T cell mitogenesis	Increased	14
	Interleukin-2 production	Increased	14
	Delayed-type hypersensitivity	Increased	14

laboratory animals. A consistently reported biologic phenomenon in the aged is an increase in free radical formation and lipid peroxidation. Enzymatic and nonenzymatic products of lipid peroxidation have been shown to decrease T cell-mediated function.<sup>9,12</sup> Given the fact that enzymatic antioxidant defenses are reduced in aging and that high levels of some antioxidants are reduced in the elderly, the aged immune system could potentially benefit from increased intake of vitamin E.

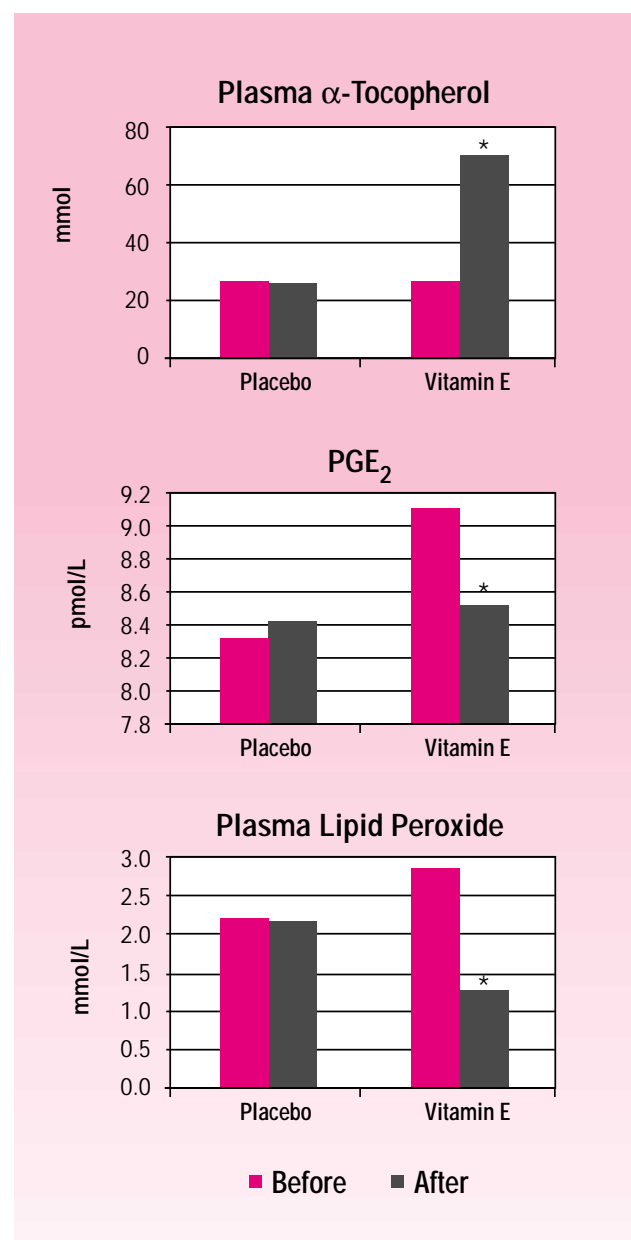
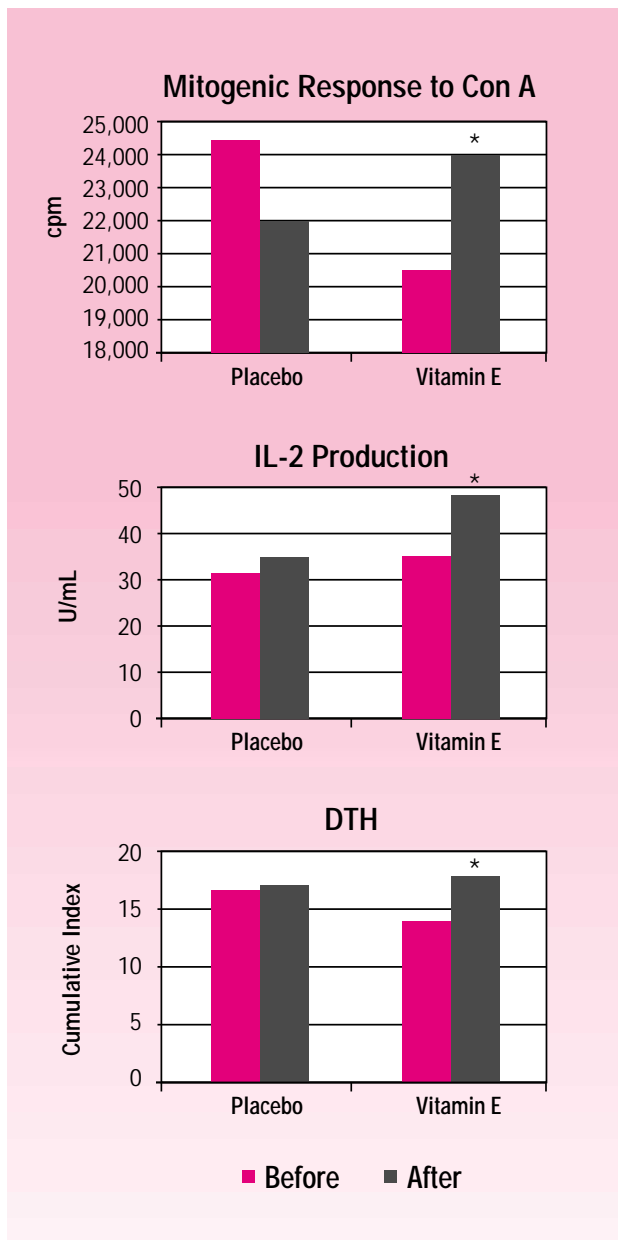
To test this hypothesis, we evaluated the effect of vitamin E supplementation on the immune responsiveness of aged mice.<sup>13</sup> In this study, the immune response of old mice fed diets containing 30 ppm or 500 ppm of dl- $\alpha$ -tocopherol acetate (vitamin E) for 6 weeks was compared with that of young mice fed 30 ppm of dl- $\alpha$ -tocopherol. Splenocytes from old mice fed 500 ppm of dietary vitamin E had a significantly higher proliferative response to Con A and lipopolysaccharide, but not to PHA, than did control animals fed 30 ppm of vitamin E. In addition, vitamin E supplementation signifi-

cantly increased DTH to 2,4-dinitro-7-fluorobenzene. This immunostimulatory effect of vitamin E was associated with increased production of IL-2 and decreased production of PGE<sub>2</sub> (Table 3).

To further test the effectiveness of vitamin E supplementation in humans, we performed a double-blind, placebo-controlled study to demonstrate that certain in vivo and in vitro indices of the immune response could be improved with vitamin E supplementation<sup>12</sup> (Figures 1 and 2).

Table 3. Effects of vitamin E on immune response of 24-month-old mice<sup>a</sup>

Parameters	30 ppm <sup>b</sup>	500 ppm <sup>b</sup>
Serum $\alpha$ -tocopherol	71	194 <sup>c</sup>
Delayed-type hypersensitivity	36 <sup>c</sup>	75
T cell lymphocyte proliferation	5 <sup>c</sup>	38
B cell lymphocyte proliferation	24 <sup>c</sup>	85
Ex vivo splenic prostaglandin E <sub>2</sub> synthesis	123 <sup>c</sup>	89
Interleukin-2	44 <sup>c</sup>	85
<sup>a</sup> Data adapted from reference 12		
<sup>b</sup> All values expressed as a percentage of a 3-month-old control group (fed 30 ppm of vitamin E)		
<sup>c</sup> Significantly different from control and other experimental groups (P $\leq$ .05)		



**Figure 1.** Effect of vitamin E supplementation on mitogen response to concanavalin A (Con A), interleukin-2 (IL-2) production, and delayed-type hypersensitivity (DTH) in elderly humans. Thirty-four elderly men and women were supplemented with either placebo or 800 IU of  $\alpha$ -tocopherol for 30 days. \*Significantly different from pre-supplementation values at  $P < .05$ . (Data adapted from reference 14.)

**Figure 2.** Effect of vitamin E supplementation on plasma  $\alpha$ -tocopherol, peripheral blood mononuclear cell (PBMC) production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), and plasma lipid peroxide values. Thirty-four elderly men and women were supplemented with either placebo or 800 IU of  $\alpha$ -tocopherol for 30 days. \*Significantly different from presupplementation values at  $P < .05$ . (Data adapted reference 14.)

In this study, 34 healthy men and women (>60 years of age) were supplemented with either a placebo-containing soybean oil or 800 mg dl- $\alpha$ -tocopherol (400 mg capsules, bid) for 30 days. The study evaluated the subjects' DTH and mitogenic response as well as IL-1, IL-2, and PGE<sub>2</sub> formation. Vitamin E supplementation was associated with increases in plasma vitamin E, DTH score, and mitogenic response to Con A and IL-2 production. In addition, vitamin E supplementation was associated with decreases in PHA-stimulated PGE<sub>2</sub> production by peripheral blood mononuclear

cells (PBMC) and plasma lipid peroxide levels. However, no effect on the mitogenic response of PBMC to PHA or IL-1 production was observed.

The immunostimulatory effect of vitamin E is associated with increased resistance to infection.<sup>6</sup> Tengerdy and colleagues<sup>15</sup> showed that supplementation with vitamin E at levels of 150 to 300 mg/kg significantly reduced *Escherichia coli*-induced mortality in chickens (from 50 to 5%). Similarly, the mortality rate of mice infected with *Streptococcus pneumoniae* type I decreased from 80 to 20%

after vitamin E supplementation.<sup>16</sup> The protective effect of vitamin E has been associated with higher antibody titer and an increase in the number of plaque-forming cells. Vitamin E was also shown to be protective against *E. coli*-induced mortality in turkeys<sup>17</sup> and pigs.<sup>18</sup> We observed a significant reduction in lung influenza viral titers of mice supplemented with 500 ppm of vitamin E for 30 days compared with infected mice that consumed adequate levels of vitamin E (30 ppm).<sup>19</sup> Others have reported protective effects

**Vitamin E supplementation appears to enhance immune response and may protect humans and laboratory animals against infections and/or disease.**

against viral infection.<sup>20-22</sup> Epidemiological studies indicate a lower incidence of infections in elderly persons with higher plasma levels of tocopherol.<sup>23</sup> Our preliminary results show reduced infection in vitamin E-supplemented elderly human and animal subjects. Thus, vitamin E supplementation appears to enhance immune response and may protect humans and laboratory animals against infections and/or

disease. Indirect evidence and preliminary results also indicate that vitamin E might protect elderly humans against infectious disease.

The mechanism of the immunostimulatory effect of vitamin E is still under investigation. Current research indicates that this effect is induced mostly through decreasing macrophage prostaglandin-induced suppression of T cells and/or decreasing free-radical formation. Although it appears that vitamin E supplementation enhances immune function in aged humans and animals, further studies are necessary to determine the direct effect of vitamin E on T cells and the exact mechanism(s) responsible for its immunostimulatory effects.

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# Senior Dog Clinical Studies

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## INTRODUCTION

Although there is some variation based on adult body size, dogs are generally considered to be “senior” when they reach seven years of age. As dogs reach their senior years, the risk of a host of conditions increases. Senior dogs are at increased risk for endocrine disorders, cardiac disease, urinary/kidney conditions, neoplasia, and obesity among others.<sup>1-3</sup>

## SIGNS OF AGING

Some of the conditions associated with aging are interrelated in terms of their etiology as well as in terms of their management. Obesity, 10–15% or more over ideal weight, is considered the most common nutritionally-related condition of the dog affecting 25% or more of the general canine population.<sup>2-5</sup> Although there may be a subset of dogs that becomes underweight with advancing age, the incidence and the severity of obesity increase as dogs reach five to seven years of age and older.<sup>2,6,7</sup>

Following an initial peak when dogs are less than 2 years old, the risk of conditions involving the joints also increase as dogs reach five to seven years of age and older.<sup>1,3</sup> In dogs, obesity has been associated with an increased incidence of articular and locomotor problems.<sup>3</sup> Although it has not been shown directly in dogs it is known that excess body weight influences the development of osteoarthritis of the hip joint in humans.<sup>8,9</sup>

Are senior dogs obese because they are less mobile? Or are senior dogs less mobile because they are obese? Of course both scenarios are plausible and likely in different individual cases involving senior dogs. Obviously, the first line of attack from the veterinary perspective is to prevent senior dogs from adding the pounds that make them obese, thus reducing their risk of developing or reducing the exacerbation of associated conditions.

Unfortunately, prevention of obesity as dogs advance into their senior years can be difficult. From the owner's perspective, development of obesity can be an insidious process because it may take place over months or years. From the veterinarian's perspective, the 5-year-old dog carrying a little extra condition could easily be obese by the time it comes back for its next vaccination. However, if the situation is assertively addressed with the clients when first noticed the onset of obesity may be prevented.

Warning clients of the potential detrimental effects of obesity may motivate some of them to take steps to prevent obesity in their pets. Despite these best efforts a substantial and growing proportion of dogs will become obese. For the subset of dogs that are obese and have osteoarthritis the benefit of weight loss on signs of lameness may be a powerful motivating factor for owners to successfully manage their dog's weight loss. Results of a recent study (described below) highlight the benefit of moderate weight loss on signs of lameness due to hip osteoarthritis in medium to large breed senior dogs.<sup>10</sup>

## CLINICAL STUDY: EFFECT OF WEIGHT LOSS ON LAMENESS

In this clinical study, nine client-owned dogs between 6 and 13 years of age were enrolled. Dogs ranged in weight from 37 to 116 pounds and were at least 12% greater than their ideal body weight at the time they started the study. All dogs had moderate signs of lameness due to hip osteoarthritis upon enrollment. Dogs were screened by physical, radiographic, orthopedic exams, and serum chemistry panels including a thyroid panel to ensure the dogs did not have any other underlying conditions contributing to their obesity (eg, hypothyroidism) or lameness (eg, ruptured cruciate ligament).

Upon successful screening, dogs began a weight loss program including Eukanuba Veterinary Diets® Nutritional Weight Loss Formula™ Restricted-Calorie/Canine fed at 60% of maintenance calories for initial body weight. Feed intakes were adjusted according to each dog's weight loss progress with further restrictions imposed if necessary to attain a weight loss rate of about 1.5% of body weight per week. The goal was to achieve at least 10% weight loss over the course of the study. Weight loss was initially monitored weekly until dogs consistently achieved their 1.5% weekly weight loss goal. Subsequent rechecks were less frequent, usually at monthly intervals. Lameness, body weight, and other evaluations were completed at the beginning, midpoint, and at the end of the weight loss period for each dog. Lameness was evaluated using a numerical rating and a visual analogue scale to record observations of lameness (**Table 1**).

**Table 1.** Visual analogue scale (above) and numerical rating scale (below) used to score lameness due to hip osteoarthritis.



Hind Limb Lameness Score	
Score	Criteria
0	Clinically sound
1	Barely detectable lameness
2	Mild lameness
3	Moderate lameness
4	Severe lameness (carries limb when trotting)
5	Could not be more lame

## Results

Body weights declined significantly over the course of the 10–19 week weight loss period with the nine dogs achieving 11–18% body weight loss. Over this same period lameness scores improved significantly (**Figure 1**). None of the dogs was withdrawn from the study because of worsening lameness.

Moderate weight loss in overweight senior dogs can result in a significant reduction in lameness due to hip osteoarthritis. Dogs in this study had a mean weight loss of 15% of initial body weight. Weight loss alone resulted in a reduction in lameness, from moderate lameness at a walk or trot at the beginning of the study to barely detectable lameness after weight loss. Although not specifically evaluated in this study, it is also possible that weight loss may slow the

progression of lameness through reduction in stresses to joints, tendons, and ligaments.

Successful weight loss programs are dependent on the involvement and commitment of the owner to achieving weight loss in their pet. Lameness is an aspect of the senior dog's health that owners are usually keenly aware of. Improvements in lameness as their dog loses weight are likely to be noticed by owners and can be used as a powerful motivational tool to achieve weight loss and to maintain their senior dog at an acceptable weight. In some cases it is also possible that treatment with nonsteroidal antiinflammatory drugs may not be needed to manage lameness following successful weight loss.

## SENIOR DOG CLINICAL STUDY: PRELIMINARY DISCUSSION

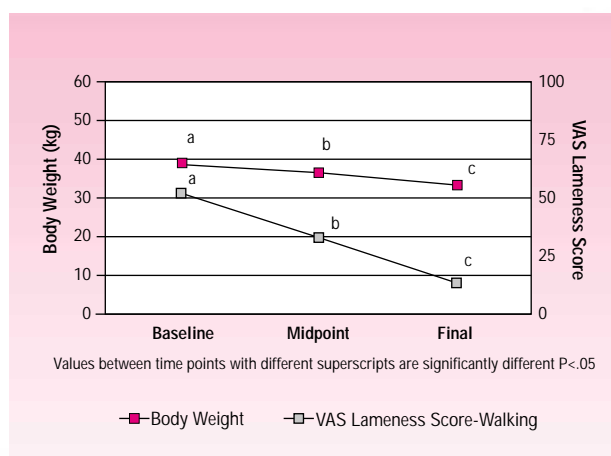
### Routine Health Care for Older Dogs

Managing obesity is just one aspect of the care of senior dogs. Routine yearly or twice yearly screening of senior dogs with physical exams and varying levels of complete blood counts and serum chemistry panels has been advocated.<sup>11-13</sup> The most important aspect of this type of yearly evaluation is to establish reference values for the individual animal as it progresses through various lifestages, but also to identify conditions early in their course before they advance and additional complications arise.

### Screening for the Study

Such screening was used to qualify 7- to 10-year-old Golden Retriever dogs for a prospective clinical study. Extremely thin (body condition score of less than 2 out of possible 5) and extremely obese dogs (body condition score greater than 4 out of possible 5) were excluded from the screening. Dogs selected for screening were thought by their owners and by their veterinarians to be healthy (ie, free from systemic disease aside from common chronic conditions such as mild osteoarthritis). Screening consisted of physical exam, complete blood count, serum chemistry panel including total and free T<sub>4</sub> by equilibrium dialysis, urinalysis, and heartworm testing. Findings based on this screening are presented in **Table 2**.

Ten percent of these apparently healthy senior Golden Retrievers had an undetected medical condition or abnormal clinical chemistry result that required additional work up or treatment. Hypothyroidism was the most common unrecognized condition, present in approximately 6% of the screened population. Hypothyroidism in these cases was suspected when total T<sub>4</sub> was less than 1 µg/dL and/or free T<sub>4</sub> by equilibrium dialysis was less than 10 pmol/L. In most cases, these analyses were confirmed at follow-up rechecks at least 2–4 weeks following the initial evaluations. In many cases, in addition to repeat measures of free T<sub>4</sub> a diagnosis of hypothyroidism was supported by additional indications such as hypercholesterolemia or other physical signs such as lethargy, unexplained weight gain or dermatologic changes consistent with hypothyroidism.



**Figure 1.** Lameness scoring (Walking; visual analog Scale described below) and body weight (kg) in 9 overweight senior dogs during weight loss. Lameness scoring was measured using a visual analogue scale ranging from 0 = “not detectable lameness” to 100 = “could not be more lame.”

**Table 2. Diagnoses/clinical findings in 200+ senior Golden Retrievers screened by physical exam, serum chemistry panel including total and free T<sub>4</sub>, urinalysis, and complete blood count.**

Findings/Diagnosis	Percentage of Cases
Hypothyroidism	5.2
Heartworm pos. (antigen)	1.7
Renal insufficiency	1.3
Renal ins. + hypothyroid	0.9
Cushings	0.4
Elevated liver enzyme (ALT)	0.4
Elevated amylase/lipase	0.4
<b>TOTAL</b>	<b>10.5</b>

Approximately 2% of screened dogs were heartworm positive by detection of heartworm antigen. An additional 2% of dogs screened had unrecognized renal insufficiency. Renal insufficiency was defined as detection of a serum creatinine greater than 1.6 mg/dL in conjunction with one or more additional signs of renal insufficiency such as elevated blood urea nitrogen or serum phosphorus or reduced urine concentrating capacity. Half the dogs with renal insufficiency were also hypothyroid. Treatment of hypothyroidism in these cases of renal insufficiency would presumably also help improve renal function. One dog was diagnosed with Cushing's Disease after additional testing including a low dose dexamethazone suppression test. The two remaining dogs had unconfirmed diagnoses related to elevated serum amylase and lipase (presumed to be pancreatitis) and elevated liver enzymes.

The screening for this study illustrates that effective yearly screening of even apparently healthy senior dogs can have a positive impact by uncovering otherwise unrecognized disease. In screening these 200+ dogs, 1 in 10 had a screening result that necessitated further work-up and in many cases therapeutic action. It is certainly likely that the proportion of dogs requiring further work up would be greater in the general population of Golden Retrievers than in this heavily prescreened group of apparently healthy Golden Retrievers.

Some screening programs for senior dogs do not advocate a complete blood count or serum chemistry panel as part of the "well" senior dog screening. However, based on our experience in screening these senior Golden Retrievers regarded as healthy, inclusion of a complete blood count, serum chemistry panel as well as other specialized testing based on breed risk of specific conditions may be warranted. In screening for this study, analysis of total and free T<sub>4</sub> were included because Golden Retrievers are known to be a high risk breed for hypothyroidism. While breed risk can help guide

selection of the screening tests that might be of greatest value, the caveat that comes with such screening is to guard against jumping too quickly to a diagnosis based on the screening test results. In the screening for this study dogs with low free T<sub>4</sub> on the screening exam were rechecked 2–4 weeks later. In addition, TSH and testing for thyroglobulin autoantibodies were completed with the final diagnosis based on current diagnostic recommendations.<sup>14,15</sup>

## CONCLUSION

Diagnostic screening of the senior dog may be easier to justify to the owner who has had many years to form a strong bond with their senior dog. Because of this, veterinary care of the senior dog can be a rewarding aspect of practice to develop from a financial aspect but also from the perspective of the variety of diagnostic and therapeutic challenges it presents. Hopefully, the results of these studies will assist in those ventures.

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# Nutritional Influences on Dental Health

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## INTRODUCTION

Although veterinary dentistry is a relatively new specialty, dental disease is one of the most common problems affecting companion animals and has been recognized for over seventy years. For example, Talbot reported in 1899 that periodontal disease affected 75% of dogs between 4 and 8 years of age.<sup>1</sup> This incidence has been subsequently confirmed in a recent review identifying 53 and 95% of dogs older than one year of age as having some degree of periodontitis.<sup>1</sup> Although there are fewer studies related to the cat, the incidence of periodontal disease has been noted to be 25 to 50% thereby documenting its importance in this species as well.<sup>1</sup> The widespread nature of dental concerns in the dog and cat mandate that awareness of the problem be increased and potentially beneficial strategies be explored.

## DENTAL DISEASE

Periodontal disease, while a very common problem, is often a very loosely applied term. It is often used in a generic manner to include non-periodontal conditions such as gingivitis. In actuality, it is defined as “disease of the

supporting structures of the teeth”.<sup>2</sup> These supporting structures serve to hold the teeth firmly in the jaw and act as a shock absorber, allowing for tearing and grinding of food without damage to the teeth or the alveolar bone that surrounds the teeth. The periodontal structures consist of the periodontal ligament (connective tissue between the root of the tooth and the socket), the gingiva, cementum, and alveolar bone. Progressive damage to the supporting structures of the teeth can result in pain, and ultimately, tooth loss.

The initial step in the progression towards periodontal disease is the formation and accumulation of plaque on the tooth surface. Any clean tooth, when exposed to saliva, immediately develops a glycoprotein layer referred to as the pellicle. Normal oral bacteria adhere to this pellicle and begin to multiply. The addition of food particles, sloughed epithelial cells, and salivary mucin to the pellicle forms dental plaque. It is often referred to as a biofilm, made up largely of aerobic, gram-positive bacteria.<sup>1,3,4</sup> Plaque forms very quickly in humans and animals, typically within hours of a dental prophylaxis. Dental plaque is a soft material, but movement of the tongue, drinking water or saliva cannot remove it. It can, however, be removed by physical abrasion such as that occurring during brushing of the teeth or chewing.

Plaque that is not removed can eventually be converted to dental calculus (tartar). Formation of calculus from plaque occurs when mineral salts in the saliva, such as calcium carbonate and calcium phosphate, precipitate out and are deposited in the plaque. The deposition of calcium typically occurs in and between bacterial remains present in the plaque. Dental calculus is a very hard deposit that is closely adhered to the tooth. It can be seen both above (supragingival) and below (subgingival) the gum line. Once formed, calculus can only be adequately removed by a professional dental prophylaxis.

## AGE AND BODY WEIGHT AS RISK FACTORS FOR DENTAL DISEASE

Numerous studies have shown periodontal disease as the most common diagnosis in companion animals. Many of these same studies have also documented a strong correlation between increased age and increased prevalence of dental disease. Prevalence from 66% to over 80% in dogs older than 6 years of age have been noted.<sup>1</sup> Eisner suggested that stresses, including advanced age, may compromise host defense systems in the oral cavity.<sup>3</sup> Another study conducted in Japan with 251 dogs demonstrated a significant correlation between greater dental calculus and increased age.<sup>5</sup> Results also indicated a higher prevalence of periodontitis associated with

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aging dogs. Periodontitis was also demonstrated to increase significantly with increasing age and decreasing body weight resulting in a markedly greater incidence of disease in the aging toy breed dog.<sup>4</sup> Smaller breeds and brachiocephalic breeds tend to have malocclusions (often resulting from rotated teeth), overcrowding and retained deciduous teeth.

Good oral hygiene therefore becomes more difficult and provides areas on teeth where plaque can form and calculus can deposit. The increased deposition of calculus and incidence of periodontal disease as age increases is further complicated by the fact that the likelihood of additional underlying health conditions increases as the animal ages. Therefore, risks associated with dental prophylaxis (ie, anesthesia) may also increase with increasing age.

## CONSEQUENCES OF POOR ORAL HYGIENE

Although supragingival calculus is primarily a cosmetic problem, it is indicative of the need for dental hygiene. Generally, this need is initially manifested visually as accumulation of calculus and(or) olfactorally as breath malodor. Breath malodor is primarily caused by bacterial metabolism of proteins in the oral cavity. Proteins are readily available in the oral cavity from food debris, saliva, epithelial cells, and blood. The presence of plaque and calculus provides a positive environment for bacterial proliferation and further metabolism of proteins leading to continued malodor. Breath malodor is typically associated with gingivitis and periodontitis.

Dental calculus, if left untreated, can lead to additional buildup of calculus on the teeth. The surface of dental calculus is rough, which allows for further accumulation of plaque on top of existing calculus. Maturation of this newly deposited plaque continues the process of calculus buildup on the teeth. As calculus continues to accumulate and extend into the gingival sulcus, the rough surface irritates the gingiva, causing inflammation of the soft tissues. Inflammation from bacterial toxins in plaque plus physical irritation from subgingival calculus causes gingivitis. The edges of the gums may begin to look hyperemic and mildly edematous. Although gingivitis is a completely reversible condition, it can become chronic if the teeth are not cleaned.

Bacteria can be trapped under a swollen gum line resulting in bacterial toxin and neutrophil accumulation and further tissue damage. The gingival sulcus eventually becomes a periodontal pocket, resulting in an oxygen-depleted atmosphere. Anaerobic bacteria begin to predominate in this environment, leading to further release of toxins and continuation of the host's inflammatory response. It is important to note that bacteria do not directly cause the tissue damage in periodontal disease. Rather, it is the host's immune system attempting to control the infection and inflammation that contributes to actual damage to the tissues. Once plaque and the resultant inflammation reach the periodontal ligament, damage to this anchoring structure can occur and periodontal disease is initiated.

Damage to the periodontal ligament is irreversible. As the disease progresses, alveolar bone erodes causing the tooth to loosen and be lost. This process of bone loss occurs over a prolonged period of time. Periodontal disease goes through active periods of tissue damage followed by quiescent periods of inactivity and healing. Untreated periodontal disease may take as long as two to five years before enough of the

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alveolar bone is destroyed to cause tooth loss.<sup>3,4</sup> It is often a silent disease that may progress without obvious clinical signs, even in the face of severe disease. Clinical signs of periodontal disease made include any or all of the following<sup>6</sup>:

- Halitosis
- Anorexia
- Difficulty eating
- Ptyalism
- Head shaking
- Behavioral changes
- Red, swollen, and/or bleeding gums
- Loose teeth
- Accumulation of plaque, calculus, and stain
- Ulcerations on gingival or oral mucosa

## DENTAL DISEASE AND ITS EFFECTS ON SYSTEMIC DISEASE

There has been much speculation in the veterinary community on the correlation between periodontal disease and other health problems in companion animals. Since periodontal disease is the most common disease affecting dogs and cats, concern is certainly warranted. Furthermore, dental disease is more common and often more severe in older animals who may also have compromised immune systems and other underlying diseases of the heart, lungs or kidneys. Diabetes has been linked to increased periodontal disease in humans but the same evidence is not present in dogs.<sup>4</sup> Several authors have cited existing evidence in the human literature regarding dental disease and the risk of heart disease, pulmonary infection, stroke, and low birth weight babies.<sup>6,7</sup> It has been noted that bacteremia occurs in some dogs and cats with dental disease, increasing after dental manipulation.<sup>1,6</sup> Healthy animals should be able to clear a transient bacteremia, but there may be cause for concern in animals under stress, with compromised immune or organ function and in older animals.

In addition to bacteremia, local host inflammatory responses to periodontal disease produce inflammatory cytokines. Since periodontal tissue is not walled off from the rest of the body, these cytokines may reach the general

circulation. It is possible that the concentration of cytokines may be high enough to produce systemic effects. One more recent study by DeBowes et al.<sup>7</sup> demonstrated a correlation between the severity of periodontal disease in dogs and histologic changes in the myocardium, renal and hepatic tissues. Additional research is required to determine if periodontal disease is a risk factor for systemic diseases in the dog and cat.

## ORAL HEALTH CARE STRATEGIES

Virtually all veterinarians agree that the single best oral health care strategy is prevention. Prevention is less costly for clients and safer for the animal. Regular professional dental prophylaxis combined with diligent home care is the key to healthy teeth and gums. Once dental disease has progressed beyond mild gingivitis, longer anesthetic times and more advanced procedures are necessary, increasing the cost to the client and stress to the animal.

A dental prophylaxis consists of several components: a complete oral examination, oral charting, scaling and polishing of the crown, and subgingival surfaces. Necessary equipment includes hand scalers, a power scaler, curettes, and polishing equipment. Power scalers include ultrasonic or sonic scalers and, although not required, are faster than hand scaling. For dogs, it is also recommended to use a preoperative rinse of dilute chlorhexidine solution to help minimize the bacteremia that occurs during a dental cleaning.<sup>8</sup> Power scaling should be used first, followed by hand scaling to gently remove residual plaque and calculus under the gumline. Polishing is recommended after planing and scaling to smooth enamel grooves and pits that occur from scaling. Lastly, supragingival and subgingival flushing removes residual pumice from polishing, which can act as an irritant to the gums.

Although periodic professional dental prophylaxis is very important to periodontal health, the importance of home care must be emphasized. During the past several years, there has been a dramatic expansion of dental products designed to make home dental care easier for the owner and more tolerable for the pet. Veterinarians agree that brushing the teeth remains the most effective means for removing plaque and preventing gingivitis. DuPont reported that tooth brushing three times weekly can prevent gingivitis in dogs.<sup>8</sup> Pet toothbrushes come in a variety of sizes and shapes to improve the efficacy of the brushing process. Finger brushes are available although some veterinarians feel that the bristles are too soft to effectively remove plaque.<sup>8,9</sup> They can, however, be used as a transition to a toothbrush. Toothpastes are available that are specifically designed for use by pets. Toothpaste facilitates plaque removal but effective brushing can be obtained without it. Other products are available that aid in plaque control, such as enzymes glucose oxidase and lactoperoxidase, which have antimicrobial activity and have been incorporated into some pet toothpastes. Chlorhexidine and zinc ascorbate are also available in topical gels or rinses.

## NUTRITIONAL ORAL HEALTHCARE

Daily brushing will help remove plaque and prevent the formation of calculus, gingivitis, and periodontal disease. However, compliance to this aggressive brushing schedule is questionable. Many veterinarians recognize that once yearly professional dental prophylaxis without home care will not effectively prevent periodontal disease.<sup>9</sup> In recent years, an increasing number of nutritional products have become available that can act as adjuncts to professional and home dental care. These products primarily rely on mechanical scraping to remove plaque from the teeth. They may help remove some plaque, but there are limitations to this strategy.

There is a long held belief that dry diets reduce the rate of plaque accumulation and gingivitis relative to dogs and cats exclusively fed wet food. A review of the literature by O'Rourke<sup>10</sup> concluded that there was evidence to suggest hard food maintained the health of the gingiva, periodontal membrane, and alveolar bone. A study by Burwasser and Hill<sup>11</sup>

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demonstrated that dogs fed soft diets tended to produce pathological changes in the gingiva as seen on histology. Egelberg conducted a study measuring plaque formation and the amount of gingival exudate in 14 dogs fed hard or soft diets.<sup>12</sup> Dogs fed the soft diet accumulated more plaque and developed more gingivitis than when they were fed the hard diet. However, a more recent study by Harvey et al.<sup>13</sup> involving 1,350 dogs did not find a significant protective effect in dogs fed dry food versus those fed semi-moist or wet food. Few studies have been done on cats, but one conducted by Studer and Stapley<sup>14</sup> demonstrated that cats fed soft food tended to accumulate calculus, develop gingivitis and halitosis. The effect of hard food on dental health may vary according to the individual animal.

Reduced calculus, gingivitis, and alveolar bone loss has been reported in dogs that chew on various items (toys, rawhides and biscuits) compared to those dogs that had little or no access to these materials.<sup>13</sup> Rawhide chews were found to have a greater effect as compared to biscuits or toys. Interestingly, the greatest protective effect on periodontal tissues was found in dogs that were fed hard food and chewed rawhide treats. Another study by Lage et al.<sup>15</sup> reported that rawhide chews removed more calculus from dog teeth compared to cereal biscuits. The influence of other types of chews on plaque, calculus, and gingivitis has been investigated as well. One study involving a flexible urethane bone found less supragingival calculus in dogs after 30 days of use compared to those that did not have the bone.<sup>16</sup> Another

chew developed for dental health was the subject of two studies. Both found that adding the chew to a hard diet decreased calculus, plaque, and the incidence and severity of gingivitis in dogs after three or four weeks.<sup>17,18</sup>

The introduction of several nutritionally complete diets formulated to improve oral health has occurred over the last several years. The standard strategy involves using mechanical scraping action to clean the teeth. This has primarily been achieved by changing the texture and size of the kibble. These changes are claimed to increase and prolong the chewing action by the pet. While the pet chews the food, it is purported that plaque and calculus are scraped off the surface of the teeth. Additives in some diets, such as alfalfa meal and cranberry extract are alleged to have antibacterial effects for reduction of breath malodor.

Despite reports of plaque and calculus removal by standard dental products, there are limitations to this strategy. Mechanical abrasion from hard food, chews, and specialized diets will only occur where the food actually contacts the tooth surface. Uniform results will not be obtained on all teeth and may be particularly hindered in animals with malocclusion. Additionally, the physical abrasive action can only occur while the dog or cat is actually chewing the product. There is no continued effect on the teeth once the product is swallowed, between meals or between chewing sessions. Effectiveness will also be decreased in dogs or cats that tend to swallow with little or no chewing action.

## NOVEL NUTRITIONAL APPROACH TO CONTROLLING DENTAL CALCULUS

A new approach to the prevention of tartar in companion animals is to utilize nutritional mineral sources in a way such that they can provide dental benefits. Specifically, nutritional sources of phosphates can be manipulated during manufacturing to enhance the physical properties of the kibble without altering the base formula, or kibble size. This is accomplished via a unique manufacturing procedure that coats the polyphosphates on the outer surface of the food in a microcrystalline form.

The polyphosphate crystals help to prevent the mineralization of plaque into calculus by forming a physical barrier on the plaque surface. This is in contrast to current methodologies that utilize abrasion to remove plaque during mastication. The benefit of the barrier approach is that polyphosphates can provide whole mouth benefits as they release from the diet during mastication and carry throughout the oral cavity. This mechanism of action allows the polyphosphates to provide benefits to

non-chewing surfaces as well as contact surfaces. Additionally, this nutritional approach offers a prolonged dental benefit as the polyphosphates remain within the plaque until the body absorbs them as phosphorous nutrients.

## EFFECTS OF PHOSPHOROUS SOURCES ON DENTAL HEALTH

Studies were conducted on both canines and felines to test if nutritional sources of phosphate could be utilized to improve dental health. The studies were of a crossover design, and utilized the guidelines set forth by the Veterinary Oral Health Council for determining dental benefits. In all studies, comparison diets were prepared on the same manufacturing date to ensure that no base ingredient differences existed in the formulations other than the polyphosphate coating. To ensure no product had a mechanical advantage, each dental diet was prepared with the same shape and thickness as the corresponding control.

All testing was conducted in adult animals with normal dentition. Animals were stratified into two groups with diets randomly assigned to each group. Prior to study initiation, all animals received prophylaxis to remove all supra- and subgingival calculus deposits and plaque accumulation. Following prophylaxis, diets were fed in amounts calculated to maintain body weight. After 28 days, animals were scored for calculus coverage and underwent prophylaxis followed by exposure to second diet. The utilization of a polyphosphate coating did not impact animal body weight or diet consumption. Separate studies also showed no difference in calcium or phosphorous absorption or blood chemistry. The effect of diet on calculus accumulation is shown in **Tables 1** and **2**.

**Table 1. Average dental calculus in dogs fed diets with or without polyphosphate (n=21)**

Diet	Average calculus score per tooth	Percentage reduction
Eukanuba® Adult Maintenance	1.60	—
Eukanuba® Adult Maintenance with polyphosphate	0.72*	55%
* Statistically significant at P<.05		

**Table 2. Average dental calculus in cats fed diets with or without polyphosphate (n=18)**

Diet	Average calculus score per tooth	Percentage reduction
Eukanuba® Chicken & Rice	0.80	—
Eukanuba® Chicken & Rice with polyphosphate	0.44*	45%
* Statistically significant at P<.05		

## SUMMARY AND CONCLUSIONS

Nutrition can play a key role in dental health. The consistency of a diet, as well as the nutritional components can affect the rate of calculus accumulation. Given that overall health problems increase with age, it is essential that not only dental but also all age-related problems be addressed on a daily basis through diet. With special care in manufacturing, mineral components can be utilized to provide daily dental benefits without altering kibble size or nutritional value. Research has shown that this approach can provide dramatic reductions in dental calculus accumulation rates. More importantly, this nutritional solution can be incorporated into a broad array of products such that any lifestyle/life stage for companion animals can be addressed along with dental concerns.

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