

**Clinical and Nutritional Aspects of  
Managing Gastrointestinal Health,  
Diabetes, and Obesity**



**Proceedings from a  
Pre-Congress Symposium at the  
28th World Congress of the  
World Small Animal  
Veterinary Association**

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IN MEMORIUM  
Sean M. Murray, PhD

The Iams Company and the scientific community experienced a major loss with the unexpected passing of Dr. Sean Murray on June 5, 2003. Since joining the Iams Research & Development team in 1999, Sean was a bright shining star who touched everyone he met with his energy, positive attitude, and great ideas. With a constant smile and contagious sense of humor, Sean was a natural leader who patiently encouraged others and challenged each person to strive for excellence in both work and personal achievements.

Dr. Murray was an outstanding researcher, dedicated to improving the lives of dogs and cats. He was an alumnus of the University of Illinois where he received his BS in Animal Science in 1992, his MS in Nutrition in 1997, and his PhD in Companion Animal Nutrition in 1999. Sean's research studies focused on diabetes and obesity management, as well as clinical studies. He was a well-known speaker at Iams-sponsored events from Dayton, Ohio to Japan.

Dr. Murray was a tangible example of a life well-balanced between career, family, and friendships. In his short 32 years, Sean touched the lives of countless individuals who are all the richer for having known him.

This *Proceedings*, which includes two of Dr. Murray's research publications, is dedicated to his memory.

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# Summary of Contents

## CHAPTER 1: ADVANCES IN DIETARY MANAGEMENT OF GASTROINTESTINAL DISEASE

### Stanley L. Marks

Pages 12-16

#### Summary.

The disciplines of nutrition and gastroenterology are intimately related by virtue of the primary role played by the gastrointestinal tract in the assimilation of food. The therapeutic approach to most gastrointestinal diseases involves a combination of pharmacologic and nutritional therapy. Unfortunately, the beneficial impact of nutritional therapy is often ignored in many patients, resulting in incomplete or delayed resolution of signs. Restriction or manipulation of individual dietary components is perhaps the single most important factor in the treatment of either acute or chronic gastrointestinal disturbances. Despite these recommendations, there is a paucity of information pertaining to the nutritional requirements of dogs and cats with gastrointestinal disorders.

#### Findings.

##### Dietary Fat

- A fat-restricted diet is important in the management of a variety of gastrointestinal diseases in dogs
  - Fat delays gastric emptying
  - Fat-restricted diets appear to be better tolerated in a variety of gastrointestinal diseases
- Modifying dietary ratio of omega-6:omega-3 fatty acids
  - May reduce inflammatory response
  - Use of a fish oil-supplemented diet (increased omega-3 fatty acids) in the therapy of ulcerative colitis revealed
    - 35 to 50% decrease in neutrophil production of LTB<sub>4</sub>
    - Significant improvement in clinical signs and histologic appearance of the rectal mucosa
    - Suppression of IL-1 and platelet activating factor synthesis and scavenging of free oxygen radicals
  - Healthy dogs fed diets with omega-6:omega-3 fatty acid ratios of 5:1 to 10:1 demonstrated
    - Decreased production of LTB<sub>4</sub> (inflammatory) and increased production of LTB<sub>5</sub> (less inflammatory) in plasma, neutrophils and skin
    - Increases in certain long-chain omega-3 fatty acids and decreases in arachidonic acid in the small intestine and colonic mucosa

##### Dietary Protein

- Adverse reactions to dietary staples are common in cats and dogs with chronic gastrointestinal disease
  - Can often be successfully managed by feeding selected-protein diets
  - High prevalence of adverse reactions to foods in cats with chronic gastrointestinal problems was found
  - Highly digestible commercial diets, without novel protein sources, have also been shown to be effective in the management of patients with large-bowel diarrhea.

##### Dietary Fiber

- Moderately fermentable fiber sources are frequently recommended for the treatment of chronic colitis
  - Beet pulp, a moderately fermentable fiber, has been shown to provide an adequate amount of SCFAs as well as promote good stool quality in cats
- Fructooligosaccharides (FOS)
  - Added to diets of healthy cats at 0.75% (dry matter) increased the numbers of fecal lactobacilli and reduced the numbers of fecal *Clostridium perfringens*
  - German Shepherd Dogs supplemented with FOS at 1.0% (as fed) of their diet had potentially beneficial changes in duodenal bacterial flora
- Mannan oligosaccharides (MOS)
  - Potential beneficial effect in altering the intestinal flora
  - Helps prevent binding of pathogenic bacteria to specific residues (eg, mannose) on the enterocyte

#### Application.

Diets such as Eukanuba Veterinary Diets<sup>®</sup> Low-Residue<sup>™</sup> Adult/Canine or Feline Formula, which contain features such as beet pulp, fructooligosaccharides (FOS), mannan oligosaccharides (MOS), and an adjusted fatty acid profile, can be useful in nutritionally managing animals with certain types of gastrointestinal disorders.

## CHAPTER 2: GASTROINTESTINAL DIAGNOSTICS

**Jörg M. Steiner**

Pages 17-24

### Summary.

Clinicians are challenged on a daily basis to arrive at a definitive diagnosis in order to specifically treat their patients with gastrointestinal disorders. In general, diagnostic tests can be divided into the following three groups: 1) those that are aimed at confirming the presence of an etiologic agent, 2) those that assess morphology, and 3) those that assess function.

### Findings.

**Diagnostic tests that assess etiology (eg, fecal tests for parasites, bacteria, and viruses)**

- Usefulness is hampered by the fact that many gastrointestinal disorders are idiopathic
- Few new diagnostic tests have been introduced over the last decade

**Diagnostic tests that assess morphology (eg, imaging techniques)**

- Newer techniques (eg, computed tomography, magnetic resonance imaging) more commonly used in research rather than in veterinary patients
- Lack of progress is most likely due to
  - Limited availability of these technologies
  - The need for the patient and the diagnostic modality to be in the same location
  - High cost per each examination

**Diagnostic tests that assess function (eg, serum bile acid, cobalamin, folate, and trypsin-like immunoreactivity concentrations)**

- Several new diagnostic tests have been introduced over the last few years

**The clinical usefulness of diagnostic tests is dependent on many factors, including**

- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value

## CHAPTER 3: INFLAMMATORY BOWEL DISEASE AND PANCREATITIS IN CATS

**Margie Scherk**

Pages 25-31

### Summary.

Inflammatory Bowel Diseases (IBDs) are a diverse group of gastrointestinal disorders, which have been grouped together based on their histopathological commonalities. This is somewhat unfortunate in that the tendency is to see IBD as a diagnostic endpoint, with a sole treatment protocol, rather than as a description of a pathophysiologic response.

Acute pancreatitis is short term, completely reversible, and without fibrosis on biopsy evaluation. Chronic pancreatitis is a long-term inflammation of the pancreas associated with irreversible histopathological changes, primarily fibrosis. Most of what is seen in cats is the latter, which isn't curable; however, it can generally be controlled and is less fatal than severe necrotizing pancreatitis.

### Findings.

#### Inflammatory Bowel Diseases

- Clinical signs vary with location of the inflammatory process
  - Duodenal and gastric lesions: vomiting and weight loss
  - Small intestinal or colonic: diarrhea +/- weight loss (if small intestinal).
- History
  - Chronic, intermittent problems, which may have been going on for weeks to years
  - Prevalence increases with age
- Management
  - Suppress/modulate the immune system and eliminate coexisting protozoal and anaerobic infection using metronidazole (Flagyl™)
  - Omega-3 fatty acids should be considered, to interfere with arachidonic acid cascade, thus reducing the inflammatory response
    - Corticosteroids should be considered next, using decreasing dosages

#### Pancreatitis

- Incidence of pancreatitis is higher than previously believed
  - Incidence reported as high as 3.5% of necropsied cats
  - Statistically, 38% of cats diagnosed with hepatic lipidosis had concurrent acute pancreatitis
- Management
  - Supportive care
  - Concurrent problems (such as lipidosis or enteritis) should be addressed as well
  - Feed, rather than fast, those patients suspected of (or confirmed as) having pancreatitis
    - Unless they are vomiting
      - DO NOT fast even vomiting cats for longer than 48 hours
      - Utilize antiemetics as necessary
      - Total parenteral nutrition or jejunostomy tube feeding may be needed for intractably vomiting cats
    - Feed a balanced, non protein-restricted diet
- Prognosis depends on
  - Type of pancreatitis
  - Degree of duration and severity
  - Many cats have chronic, low-grade smoldering pancreatitis and live long lives, but do better with appropriate management

## CHAPTER 4: DIETARY MANAGEMENT OF GASTROINTESTINAL ISSUES AND OBESITY IN DOGS AND CATS: CLINICAL STUDIES

**Mark A. Tetrick**

Pages 32-36

### Summary.

Gastrointestinal issues are a top-5 complaint among pet owners and a top reason for presentation of dogs and cats to veterinarians, accounting for between 20 and 25% of veterinary visits. Among cat owners the top digestive-related health complaint has been reported as production of hairballs. For dogs, stress can be a trigger of gastrointestinal upset resulting in diarrhea. Dietary management can have an important role in managing stress-related diarrhea.

Obesity is considered to be the most common nutrition-related condition in companion animals. Dogs are often presented for conditions that may be predisposed to or that are exacerbated by obesity, such as hip osteoarthritis. Weight loss alone has been shown to help reduce the signs of hip osteoarthritis.

### Findings.

#### Hairballs

- In-home clinical study involving 102 cats from 47 households
  - Cats were randomly assigned to one of two diets in a double-blinded study
    - Control (Iams Original™)
    - Test (Iams Hairball Care™—essentially Iams Original™ plus added fiber blend)
  - Feeding the test diet resulted in
    - 22% reduction in mean number of total hairballs/week (from 2.2 to 1.7)
    - 21% reduction in vomiting (from 3.8 to 3.0 times/week)

#### Diarrhea

- 20 dogs entering an animal shelter that had or developed diarrhea within the first 36 hours were fed one of two dog diets
  - Eukanuba Veterinary Diets® Nutritional Intestinal Formula™ Low-Residue™ Adult/Canine (Low-Residue™)
  - Hill's® Prescription Diet® i/d®
- In the dogs fed Low-Residue™, diarrhea
  - improved more quickly (3 days vs. 6 days)
  - resolved sooner (8 days vs. 13 days)

#### Hip Osteoarthritis and Obesity

- When 9 client-owned dogs, at least 10% over ideal weight, with hip osteoarthritis were fed a diet (Eukanuba Veterinary Diets® Restricted-Calorie™/Canine) providing 60% of maintenance calories for 10 to 19 weeks
  - Weight loss ranged from 11 to 18%
  - Body condition improved significantly
  - Numerical rating of lameness improved significantly
  - Visual assessment scores for lameness improved by 76%

### Application.

Diets for cats designed to reduce hairballs, such as Iams Hairball Care™, can reduce the frequency of hairballs and vomiting. Eukanuba Veterinary Diets® Nutritional Intestinal Formula™ Low-Residue™ Adult/Canine was more effective in nutritionally managing stress diarrhea than Hill's® Prescription Diet® i/d®. A satisfactory rate of weight loss and improvement in lameness were achieved in dogs with hip osteoarthritis using Eukanuba Veterinary Diets® Restricted-Calorie™/Canine fed at 60% of maintenance calories for current body weight.

## CHAPTER 5: COMMON COMPLICATIONS OF INSULIN THERAPY

**Richard W. Nelson**

Pages 37-42

### Summary.

Establishing an effective treatment regimen for diabetes mellitus is often challenging in cats. Variation in factors such as pathophysiology, pharmacology, and existence of concurrent disease, can affect the success of treatment and lead to confusion and frustration for the veterinarian and owner. The author's recommended management protocol includes either lente insulin or PZI at a dosage of 1 to 2 U per cat administered twice daily and concurrent dietary therapy.

### Findings.

- **Two most important factors dictating insulin dependency in diabetic cats**
  - The severity of destruction of pancreatic beta cells
  - The presence, severity, and reversibility of concurrent disorders that negatively affect insulin sensitivity
- Most common explanation for sudden loss of glycemic control in a previously stable diabetic cat is development of a concurrent disorder causing insulin resistance
- Single biggest problem affecting accuracy of blood glucose measurements in cats is hyperglycemia induced by stress, aggression or excitement
  - Stress can
    - Override the blood-glucose lowering effect of insulin
    - Cause high blood glucose concentrations
    - Lead to poor control of glycemia
- No single type of insulin is routinely effective in maintaining control of glycemia, even with twice-a-day administration.
  - Ultralente insulin
    - Has to be administered twice a day in most diabetic cats
    - Absorption is inadequate for controlling glycemia in approximately 25% of cats
  - Lente and NPH
    - Duration of effect can be considerably shorter than 12 hours in some diabetic cats
  - Protamine-zinc insulin (PZI)
    - Glucose nadir occurs within 9 hours of administration in >80% of treated diabetic cats
    - In a recent study, use of PZI significantly improved control of glycemia in newly diagnosed diabetic cats and poorly controlled diabetic cats previously treated with ultralente or NPH insulin
  - Insulin glargine
    - Is a long-acting insulin analog
    - Slow sustained release of insulin glargine results in a relatively constant concentration/time profile over a 24-hour period
    - A preliminary study involving healthy cats showed that insulin glargine had pharmacokinetic/pharmacodynamic properties similar to that of PZI



## CHAPTER 6: NUTRITIONAL MANAGEMENT OF GLYCEMIA AND DIABETES

Sean M. Murray<sup>†</sup> and Gregory D. Sunvold

Pages 43-49

### Summary.

A nutritional approach to controlling glycemia and managing diabetes in dogs and cats includes diets formulated to contain lower levels of fat that promote normalization of the pet's glycemic response. Other nutrients that may increase efficiency of glucose metabolism and help to reduce insulin resistance include certain types of starch and fiber, chromium, and vitamin A. A consideration of the feeding regimen used with susceptible cats may also be important.

### Findings.

- Distribution of carbohydrate, protein, and fat can affect blood glucose and insulin concentrations
  - When 24 healthy normal-weight adult cats were randomly assigned to be fed a high-fat, high-protein or high-carbohydrate diet
    - Cats fed the high-carbohydrate diet had significantly higher mean total and peak glucose values
    - Cats fed the high-fat diet had higher insulin:glucose ratio, which may indicate reduced insulin sensitivity
- Starch source affects postprandial blood glucose response
  - When 30 weight-stable dogs and 30 weight-stable cats were randomly assigned to a diet containing different starch sources for 10 weeks
    - Dogs and cats fed the diet containing rice had the highest postprandial glucose response and plasma insulin levels
    - Dogs fed the diet containing sorghum had the lowest postprandial glucose response
    - Dogs fed the diet containing barley had the lowest postprandial plasma insulin
    - Cats fed diets containing wheat, barley or corn had the lower postprandial glucose responses and plasma insulin levels
- Feeding regimen may affect postprandial insulin response
  - Cats fed ad libitum had a 40% greater response in blood insulin after a test meal than cats fed several small meals/day

### Application.

Eukanuba Veterinary Diets<sup>®</sup> Optimum Weight Control contains nutrients that affect the metabolic and physiologic changes that may occur during diabetes. The use of these nutrients in the diet may result in better management of glycemic response and help reduce insulin resistance.

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<sup>†</sup> Deceased.

## CHAPTER 7: NUTRITIONAL MANAGEMENT OF WEIGHT IN DOGS AND CATS

Gregory D. Sunvold and Sean M. Murray<sup>†</sup>

Pages 50-55

**Summary.** New and innovative approaches to weight management diets for dogs and cats include the use of reduced-fat diets that contain normal levels of appropriate fiber sources, in contrast to traditional diets that contained excessive levels of non-fermentable fiber. In addition, the inclusion of novel weight-modulating nutrients, such as certain starches, chromium, L-carnitine, and vitamin A, addresses the physiological and metabolic alterations associated with obesity. Diets formulated for weight loss that contain these nutrients have been demonstrated to enhance weight management, while preserving lean body mass (LBM) and promoting health.

**Findings.** Certain nutritional components can be useful in helping promote a more normal glycemic response in dogs and cats

- Starch source affects postprandial blood glucose response
  - Overweight dogs fed a weight loss diet containing corn and sorghum for ten weeks lost more weight and had a lower body fat percentage than those fed diets with corn and wheat or corn and rice
- Fermentable fiber may decrease postprandial hyperglycemia by
  - Slowing digestion and absorption of carbohydrates, which reduces hyperglycemia after a meal
  - Altering secretion of gastrointestinal hormones that control nutrient metabolism, increasing glucose removal from the bloodstream
  - Improving the timing of insulin release in response to a glucose load
- Chromium
  - Is an important modulator of insulin function
  - Helps preserve lean body tissue during weight loss
- L-Carnitine may
  - Promote greater weight loss
  - Facilitate greater fat loss
  - Help control appetite and lead to voluntary reduction in intake
- Blood levels of leptin are affected by obesity in dogs and cats
  - Leptin helps to regulate and maintain the degree of obesity
  - Dogs and cats fed supplemental vitamin A resisted weight gain
  - In a study with overweight dogs fed a diet formulated for both weight loss and glycemic control versus a traditional high-fiber, weight loss diet
    - Dogs fed each of the diets lost weight
    - Dogs fed the glycemic-control diet
      - Lost 50% more body fat
      - Had higher percentage of LBM
      - Showed improved measures of glucose metabolism

### Human-pet relationship can assist in weight loss

- A pilot study using overweight caregivers and overweight pets in a joint weight loss and exercise program over 6 months revealed that
  - 82% of dogs and 55% of humans lost weight
  - Dogs that lost weight lost an average of 10% of their body weight
  - Caregivers reported that dogs had improved quality of life and overall health and increased energy levels

**Application.** Eukanuba Veterinary Diets<sup>®</sup> Restricted-Calorie<sup>™</sup> and Optimum Weight Control diets contain nutrients that effect the metabolic and physiologic changes that occur during obesity. The use of these nutrients in the diet may result in more effective weight loss. As part of a total weight management program, Restricted-Calorie<sup>™</sup> Canine and Feline Formulas provide a safe and effective way to promote weight loss in dogs and cats.

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<sup>†</sup> Deceased.

## CHAPTER 8: CLINICAL WEIGHT MANAGEMENT FOR DOGS AND CATS

**Sharon A. Center**

Pages 56-69

### Summary.

Obesity is the most common nutrition-related health problem in companion animals in North America. Studies have estimated incidence of overweight and obese cats to range between 19 and 40% and dogs to range between 24 to 30%. Selection of diets with a low caloric density, avoidance of high-fat rations, and use of set meal times (avoiding free-choice maintenance dry foods) are useful considerations in weight loss programs. In addition, as much exercise as is reasonably possible and appropriate for the patient's health status should be encouraged.

### Findings.

- Obesity exists when body mass exceeds 120% of ideal body weight
- Obesity can be estimated by
  - Relative percentage of ideal body weight
  - Body condition scoring
  - Morphometric measurements
- Organized approach to weight loss
  - Client commitment essential
  - Baseline assessments
  - Diet history
  - Verify current energy intake
- Detailed medical history
  - Weight gain timeframe
  - Patient's acceptance and response to previous diet modifications
  - Medications
  - Baseline laboratory tests—CBC, chemistry profile, and urinalysis
- Reducing strategies
  - Specialized reducing formulas—low energy, normal or higher than normal protein
  - Introduce diet gradually over 6–10 days
  - Feed in several small meals rather than one large one or ad libitum
  - Restrict energy to 60% of daily energy requirement
  - Safe rate of weight loss is 1.0–1.25% of body weight/week
  - Reasonable maximum goal is 20–25% body weight reduction over 18 weeks
  - Snacks must have their caloric contributions calculated into daily energy allowance
  - Human behavior may need to be modified
  - Exercise is recommended
  - Energy intake may need to be titrated
- Recheck appointments
  - Every 2 weeks until appropriate energy intake is identified.
  - Then every 4 weeks until desired weight achieved
- Weight control after weight loss
  - Use maintenance diets for pet's life stage and control quantities
  - Modification of sedentary lifestyle and continued exercise recommended

### Application.

An organized approach to weight loss and owner understanding and participation can greatly improve the likelihood of success. Using a diet formulated to be low in fat and have normal levels of protein can help conserve lean body mass during weight loss. After weight loss, maintenance of healthy body weight can be achieved by controlling amount fed and using a diet formulated for the proper life stage.

# Author Profiles



## **Sharon A. Center, DVM, Diplomate ACVIM**

Dr. Center obtained her DVM from the University of California at Davis and thereafter completed a Small Animal Internship at Cornell University. After working for several years in private practice in California, she returned to Cornell to complete a residency in Small Animal Internal Medicine. Dr. Center joined the clinical faculty at Cornell in 1982 where her responsibilities include co-management of the Internal Medicine Referral Service in the Companion Animal Hospital, didactic teaching of veterinary students, and conductance of focused research. She is currently a Professor of Internal Medicine at Cornell where she actively pursues research focused in the area of hepatobiliary disease. A particular interest in her research is feline metabolism and the hepatic lipidosi syndrome.



## **Stanley L. Marks, DVM, PhD, Diplomate ACVIM**

Dr. Marks graduated from the University of Pretoria, South Africa in 1986 and completed an internship in small animal medicine and surgery at the University of Missouri, Columbia in 1987. He completed a small animal internal medicine residency program at the University of Florida and an oncology residency program at the University of California, Davis. Dr. Marks received his PhD in nutrition from the University of California, Davis, where he is currently Associate Professor of Medicine in the Department of Medicine and Epidemiology. Dr. Marks is a Diplomate of the American College of Veterinary Internal Medicine (ACVIM) in the subspecialties of internal medicine and oncology, and a Diplomate of the American College of Veterinary Nutrition (ACVN). His research interests are in the area of small animal gastroenterology, with an emphasis on dietary modulation of intestinal mucosal barrier function and bacterial gastroenteritis.



## **Richard W. Nelson, DVM, Diplomate ACVIM**

Dr. Nelson received a DVM from the University of Minnesota, was an intern and resident in small animal internal medicine at Washington State University, and is board certified in internal medicine. He was Associate Professor at the Department of Veterinary Clinical Sciences, School of Veterinary Medicine at Purdue University. He is currently a Professor in the Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California at Davis. Dr. Nelson's research interests are in the area of small animal clinical endocrinology, most notably the endocrine pancreas, thyroid gland, and adrenal gland. A primary research focus has involved evaluating the role of dietary fiber in treating diabetes mellitus in dogs and cats.



## **Dr. Margie Scherk, DVM, DABVP**

Dr. Margie Scherk is a private practitioner and founder of Cats Only Veterinary Clinic in Vancouver, British Columbia, Canada. She is board certified in the specialty of feline practice by the American Board of Veterinary Practitioners. Dr. Scherk graduated from the University of Guelph in 1982 with a DVM from the Ontario Veterinary College. She is an active member of the American Association of Feline Practitioners (AAFP), a member of the Academy of Feline Medicine, past-Editor of the *AAFP Newsletter*, and co-editor of the *Journal of Feline Medicine and Surgery*. She recently served on the AAFP/AFM Feline Vaccine Recommendations Panel. She pioneered the use of the transdermal fentanyl patch for the alleviation of pain in companion animals. In 1997, Dr. Scherk was named the Canadian Veterinary Medical Association Small Animal Practitioner of the Year.



### **Jörg M. Steiner, med.vet., Dr.med.vet., PhD, DACVIM, DECVIM-CA**

Dr. Steiner received his veterinary degree from the Ludwig-Maximilians University in Munich, Germany in 1992. He did an internship in small animal medicine and surgery at the University of Pennsylvania from 1992 to 1993 and a residency in small animal internal medicine at Purdue University from 1993 to 1996. He received his Dr.med.vet. degree from the Ludwig-Maximilians University in 1995 in recognition of research on feline trypsin and feline trypsin-like immunoreactivity. In 1996 he achieved board certification with the American College of Veterinary Internal Medicine and the European College of Veterinary Internal Medicine. In 2000 Dr. Steiner received a PhD from Texas A&M University for his work on canine digestive lipases and their use for the diagnosis of gastrointestinal disorders in the dog. He currently serves as Clinical Assistant Professor with the Department of Small Animal Medicine and Surgery at Texas A&M University. Together with Dr. David A. Williams, Dr. Steiner serves as co-director of the GI Laboratory and is involved in the development of new diagnostic tests for disorders of the gastrointestinal tract.



### **Gregory D. Sunvold, PhD**

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 1994. The title of his PhD thesis was Utilization of Selected Dietary Fibers by Dogs and Cats. Dr. Sunvold joined the Strategic Research group in the Research and Development Division at The Iams Company in 1994 where he is currently Director of Clinical Research and Intellectual Properties. 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**

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, weight management, and senior animal health.

# Advances in Dietary Management of Gastrointestinal Disease

**Stanley L. Marks, BVSc, PhD,  
Diplomate ACVIM (Internal Medicine,  
Oncology), Diplomate ACVN**

*Department of Medicine and Epidemiology  
University of California, Davis, California USA*

## INTRODUCTION

The disciplines of nutrition and gastroenterology are intimately related by virtue of the primary role played by the gastrointestinal tract in the assimilation of food. The therapeutic approach to most gastrointestinal diseases involves a combination of pharmacologic and nutritional therapy. Unfortunately, the beneficial impact of nutritional therapy is often ignored in many patients, resulting in incomplete or delayed resolution of signs. Restriction or manipulation of individual dietary components is perhaps the single most important factor in the treatment of either acute or chronic gastrointestinal disturbances. Despite these recommendations, there is a paucity of information pertaining to the nutritional requirements of dogs and cats with gastrointestinal disorders. This paper will focus on dietary advances for the management of chronic small- and large-bowel disease in dogs and cats.

## CHRONIC SMALL AND LARGE BOWEL DISEASE

Dietary modification is essential for the management of most patients with chronic small-bowel disease. Dogs with diarrhea associated with small-bowel disease should be managed with a diet that is highly digestible, moderately fat-restricted, lactose-free, and gluten-free. There is varied opinion regarding the importance of feeding select-protein diets containing novel, single protein sources to which the animal has not been previously exposed. The theoretical concerns with the “abrasive” effects of dietary fiber on the inflamed intestinal tract and the presumed negative effects of fiber on small intestinal assimilation of nutrients should be reconsidered because the gelling and binding properties of fiber and the effects of fermentation appear to be beneficial in certain small intestinal diseases.<sup>1</sup>

Less information is known about the nutritional recommendations for the management of chronic diarrhea associated with feline small-bowel disease. In contrast to dogs, cats with small-bowel disease seem to tolerate diets containing higher levels of fat,<sup>2</sup> and high-fat diets (79% fat calories) do not appear to delay gastric emptying in the cat.<sup>3</sup>

*Duodenal biopsy showing villous blunting and moderate lymphoplasmacytic enteritis in a dog with inflammatory bowel disease*

Dietary recommendations for the management of diarrhea associated with large-bowel disease are controversial because the veterinary information is often derived from few data-based refereed publications and many uncontrolled clinical observations. The response to dietary therapy can vary dramatically from one patient to another, with some animals showing improvement on low residue, “hypoallergenic” diets,<sup>4-6</sup> and others improving on less digestible diets containing moderately fermentable or poorly fermentable fiber sources.<sup>7</sup>

## Dietary Fat

A fat-restricted diet is important in the management of a variety of gastrointestinal diseases in dogs, even though fat

is a valuable caloric source and enhances the palatability of the diet. Fat delays gastric emptying,<sup>8,9</sup> and fat-restricted diets appear to be better tolerated in a variety of gastrointestinal diseases. The assimilation of dietary fat is a relatively complex process and malabsorbed fatty acids are hydroxylated by intestinal and colonic bacteria. These hydroxy-fatty acids stimulate colonic water secretion and exacerbate diarrhea and fluid loss.<sup>10</sup> Fat malassimilation can also be associated with malabsorption of bile acids, resulting in deconjugation of unabsorbed bile acids and increased mucosal permeability and secretion.<sup>11</sup>

## Fatty Acids

Manipulation of the dietary ratio of omega-6 (n-6) to omega-3 (n-3) polyunsaturated fatty acids (PUFA's) has the potential to reduce the inflammatory response in human ulcerative colitis and Crohn's disease patients.<sup>12,13</sup> Diets enriched in n-3 fatty acids can result in the incorporation of the n-3 fatty acids into biological membranes, with a corresponding decrease in concentrations of the proinflammatory n-6 fatty acids such as arachidonic acid (20:4,n-6). The therapeutic potential of dietary precursor modulation by a fish-oil-supplemented diet (n-3 fatty acids), such as eicosapentaenoic acid (C20:5,n-3) and docosahexaenoic acid (C22:6,n-3) in the therapy of ulcerative colitis has been shown to result in a 35% to 50% decrease in neutrophil production of LTB<sub>4</sub>.<sup>12</sup> Significant improvement in symptoms and histologic appearance of the rectal mucosa has been observed in several small series of patients with Crohn's disease and ulcerative colitis given fish oil at 3 to 4 g daily for 2 to 6 months in uncontrolled studies.<sup>13</sup> However, a larger, randomized, double-blind trial comprising 96 patients with ulcerative colitis failed to reveal any benefit in remission maintenance or treatment of relapse on 4.5 g of eicosapentaenoic acid daily, despite a significant reduction in LTB<sub>4</sub> synthesis by blood peripheral polymorphonuclear cells.<sup>14</sup> It should be emphasized, however, that the antiinflammatory actions of the fish oils, in addition to inhibition of LTB<sub>4</sub>, include suppression of IL-1 and platelet activating factor synthesis and scavenging of free oxygen radicals.<sup>14</sup>

Studies in healthy dogs fed diets with n-6:n-3 fatty acid ratios of 5:1 to 10:1 demonstrated a decreased production of LTB<sub>4</sub> in plasma, neutrophils and skin, and increased production of the less inflammatory leukotriene B<sub>5</sub> in plasma and neutrophils.<sup>15</sup> Increases in certain long-chain n-3 fatty acids and decreases in arachidonic acid were identified in the small intestine and colonic mucosa of healthy Beagles fed the same ratios.<sup>16</sup> Further research is warranted to determine the clinical benefits of fatty acid manipulation in dogs and cats with inflammatory bowel disease. The impact of increased lipid peroxidation after fish oil supplementation should be considered when altering the n-6:n-3 fatty acid ratio.<sup>17</sup> Antioxidant supplementation may be able to counteract the potentially adverse effects of n-3 fatty acids.

*Endoscopic appearance of the colon from a dog showing marked erythema due to inflammatory bowel disease*

## Dietary Lactose and Gluten

Intestinal disease frequently destroys or reduces mucosal brush border enzyme activity, particularly lactase, the most superficial enzyme. Milk or other lactose-containing substances should therefore be avoided in patients with enteric disease. Failure to digest lactose results in bacterial degradation of the sugar to volatile fatty acids which can cause an osmotic diarrhea. The use of yogurt as a probiotic for therapy of chronic diarrhea is not recommended because of its lactose content. In addition, probiotics should be administered frequently throughout the day to facilitate colonization in the intestine and mucosal displacement of putative pathogenic bacteria. Gluten is a component of wheat, oats, barley, and rye, all of which should be avoided in patients with inflammatory bowel disease (IBD) in the event that the diarrhea is due to a gluten enteropathy.

## Dietary Protein

Adverse reactions to dietary staples are common in cats and dogs with chronic gastrointestinal disease, and can often be successfully managed by feeding selected-protein diets.<sup>4,18-20</sup> Because antigenic determinants on proteins are occasionally incriminated as the precipitating factor in IBD, some investigators advocate the feeding of a "hypoallergenic" diet that is generally free of additives and preservatives, and contains a single, novel protein source that is highly digestible.<sup>21</sup> There are no protein sources that are inherently hypoallergenic. The protein source should be highly digestible because intact proteins are more antigenic than polypeptides and amino acids.<sup>22</sup>

There is evidence to suggest that some forms of colitis may be associated with a dietary sensitivity similar to that observed with small bowel disease.<sup>18</sup> Proteins, lipoproteins, glycoproteins, lipopolysaccharides, and carbohydrates can

induce an immunologic or inflammatory response similar to that observed in the small intestine. The theoretical benefit for utilizing highly digestible “hypoallergenic” diets for patients with colitis includes reducing the digestive challenge to the large intestine and minimizing the likelihood of dietary antigens actually reaching the colon, thus lessening the likelihood of an immunological reaction.<sup>6</sup>

Several studies in the veterinary literature suggest that some patients may benefit from diets providing novel, highly digestible protein sources.<sup>4,19,20</sup> One prospective study reported a resolution in clinical signs associated with idiopathic chronic colitis in 13 dogs fed rice and cottage cheese.<sup>4</sup> Only 2 of the dogs in that study tolerated a challenge with the original commercial diet that had been fed at the time of the onset of signs of colitis.

A recent study investigated the prevalence of adverse reactions to foods in cats with chronic gastrointestinal problems.<sup>18</sup> The diagnosis of food sensitivity was made by dietary elimination-challenge studies using commercial selected-protein diets (chicken or venison-based). Sixteen (29%) of the 55 cats with chronic idiopathic gastrointestinal problems were diagnosed as food sensitive. The clinical signs of another 11 cats (20%) resolved on the elimination diet but did not recur after a challenge with their previous diet. The most common allergens identified were beef, wheat and corn gluten. Weight loss occurred in 11 of the affected cats and large-bowel diarrhea was more common than small-bowel diarrhea. The clinical feature most suggestive of food sensitivity was concurrent occurrence of gastrointestinal and dermatological signs. Collectively, 50% of the cats fed the selected-protein diets had resolution of their clinical signs. This observation suggests that selected-protein diets should be considered an important part of the management of cats with chronic idiopathic gastrointestinal disease.

Highly digestible commercial diets, without novel protein sources, have also been shown to be effective in the management of patients with large-bowel diarrhea. In one prospective study, 11 dogs with idiopathic, chronic colitis were treated for 4 months with a commercial restricted-antigen diet containing protein sources limited to chicken and rice.<sup>6</sup> All dogs were simultaneously treated with sulfasalazine (20 to 40 mg/kg/day). Previous dietary management had been attempted in 9 of the 11 dogs, but diet histories were not provided. Within 1 month of consuming the limited antigen diet, 60% of the dogs required no sulfasalazine, or a reduced dosage than when originally presented. Within 2 months, 90% were stabilized with no drug therapy. These results are underscored by the relatively large number of dogs and cats diagnosed with inflammatory bowel disease that have failed dietary therapy utilizing diets containing novel, single, protein sources, but have shown excellent clinical responses to a commercial diet containing multiple intact protein sources, beet pulp, fructooligosaccharides (FOS), mannanoligosaccharides (MOS), and an altered fatty acid profile (Eukanuba Veterinary Diets®

Nutritional Intestinal Formula® Low-Residue™ Adult/Canine or Feline).

## Dietary Fiber

Dietary fiber is defined as plant material added to a diet that resists digestion by endogenous intestinal enzymes. Carbohydrates, cellulose, hemicellulose, pectin, gums, mucilages, and lignin are the major components of the dietary fiber group. Fiber can be utilized for its physical, fermentative, and bacterial effects on the intestinal tract. Moderately fermentable fiber sources are frequently recommended for the treatment of chronic colitis. The use of fiber sources with moderate to high fermentability in preference to low fermentability is often advocated, because bacterial fermentation of fiber produce short-chain fatty acids (SCFA) such as acetate, butyrate, and propionate. Butyrate is the principle energy source for the colonocyte, and there is increasing evidence that the SCFA may also be an important energy source for the enterocytes as well. Short-chain fatty acids may lower the colonic luminal pH, impeding the growth of pathogens.<sup>23</sup> Beet pulp, a moderately fermentable fiber, has been shown to provide an adequate amount of SCFA's as well as promote good stool quality in cats.

Prebiotics are a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the distal small intestine and colon. The dietary supplementation of fructooligosaccharides (FOS), a naturally-occurring carbohydrate source that resists digestion by the enzymes in the gastrointestinal tract, has been documented to have a “prebiotic” effect. The FOS are utilized to promote the growth of certain beneficial species of bacteria (*Bifidobacteria*, *Lactobacilli*, *Eubacteria*) and decrease the population of more pathogenic bacteria (*Clostridia*, *Enterobacteria*). The mechanisms involved in decreasing the pathogenic bacteria involve the creation of a restrictive physiological environment, competition for bacterial receptor sites, competition for essential substrates, and production of antibiotic-like substances. The addition of FOS to feline diets at 0.75% (DM) did not affect duodenal total bacterial counts, but it did increase the numbers of lactobacilli and reduce the numbers of *Clostridium perfringens* in the fecal flora of healthy cats.<sup>24,25</sup> Healthy German Shepherd Dogs believed to have bacterial overgrowth were supplemented with FOS at 1.0% (AF) of their diet.<sup>26</sup> Changes were recognized in the duodenal bacterial flora but these changes were of less magnitude than seen in normal dogs for these parameters. Mannanoligosaccharides (MOS) represents another oligosaccharide of interest for its potential beneficial effect in altering the intestinal flora. Mannanoligosaccharides helps prevent binding of pathogenic bacteria to specific residues (eg, mannose) on the enterocyte, as MOS contains mannose, and fimbriated mannose-specific pathogens may preferably bind to MOS.



*Gross appearance of colon from Boxer dog with histiocytic colitis*

## **INFLAMMATORY BOWEL DISEASE (IBD)**

The inflammatory bowel diseases (IBD) are the most common causes of chronic vomiting and diarrhea in dogs, and refer to a group of idiopathic, chronic gastrointestinal tract disorders, characterized by infiltration of the lamina propria by lymphocytes, plasma cells, eosinophils, macrophages, neutrophils, or combinations of these cells.<sup>21</sup> The diagnosis of IBD requires the comprehensive exclusion of potential causes of gastrointestinal inflammation, including intestinal parasites, small intestinal bacterial overgrowth, bacterial enterocolitis, dietary intolerances or allergies, and neoplasia.<sup>21</sup> Failure to eliminate known causes of gastrointestinal inflammation, which can mimic IBD, can result in frustration for the owner and clinician due to poor responsiveness of the animal to dietary or pharmacologic therapy.

Although the etiology of canine IBD is poorly understood, most of the evidence for proposed causes in dogs have been extrapolated from humans with ulcerative colitis and Crohn's disease.<sup>22,27-30</sup> Caution should be heeded in

making extrapolations across species, because human and canine IBD are not synonymous. Proposed causes for human IBD include defective immunoregulation of the gut-associated lymphoid tissue that may be precipitated by permeability defects,<sup>27</sup> infectious and parasitic agents,<sup>28,29</sup> and dietary allergies.<sup>22,30</sup> There is provocative evidence from clinical observations and animal models to incriminate normal luminal bacteria or bacterial products in the initiation and perpetuation of canine IBD.<sup>31,32</sup> The clinical response to hypoallergenic diets in some dogs and cats suggest that dietary factors may influence the pathogenesis of canine and feline IBD.<sup>4,18-20</sup> The term "hypoallergenic" refers to a diet that is generally free of additives and preservatives, and contains a single, novel protein source that is highly digestible.

Because the presumed pathogenesis of canine IBD involves hypersensitivity to luminal dietary or microbial antigens, therapy is aimed at removing any antigenic source of inflammation,<sup>22,31,32</sup> followed by suppression of the cell-mediated inflammatory response in the gastrointestinal tract. Unfortunately, the increased utilization of commercial lamb-based formulas has diminished its application in many "hypoallergenic" diets, necessitating the selection of more "exotic" protein sources such as kangaroo, ostrich, rabbit, and venison. It is important that the ingredients list of a potentially hypoallergenic diet be thoroughly evaluated, because diets with several protein sources (lamb, beef, rice, and wheat) are commonly marketed with a claim to hypoallergenicity. All flavored vitamins and flavored heartworm preventatives, table scraps, and raw-hide chews should be avoided during the feeding of the controlled diet.

Dogs with IBD that fail to respond to commercial "hypoallergenic" diets containing intact protein sources or diets containing fermentable fiber sources with prebiotics and altered fatty acid ratios may benefit from diets containing hydrolyzed protein sources in which the molecular weight of the polypeptide molecule is below 18,000 daltons (Purina Veterinary Diets™ HA HypoAllergenic™ Formula or Hill's® Prescription Diet Canine z/d® ULTRA and Feline z/d), or from home-cooked diets containing single novel protein and carbohydrate sources. Low serum cobalamin is a common finding in cats with IBD and cats should be treated with parenteral cobalamin supplementation to optimize response to dietary therapy. Parenteral administration of cyanocobalamin (250–500 µg per cat SC weekly for 6 weeks, then q 1–2 months) should return serum concentrations to normal.

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*German Shepherd Dog with concurrent inflammatory bowel disease and exocrine pancreatic insufficiency*

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# Gastrointestinal Diagnostics

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## INTRODUCTION

Clinicians are challenged on a daily basis to arrive at a definitive diagnosis in order to specifically treat their patients. The process of arriving at such a diagnosis involves the use of diagnostic tests. In general, diagnostic tests can be divided into the following three groups: 1) those that are aimed at confirming the presence of an etiologic factor, 2) those that assess morphology, and 3) those that assess function (**Table**).

Examples of diagnostic tests that assess etiology are fecal examinations for evidence of parasitic infestation; fecal cultures for *Salmonella spp.*, *Campylobacter spp.*, and other pathogenic microbes; and fecal tests for *Parvovirus* antigens. While these tests are used on a daily basis, their usefulness is hampered by the fact that many gastrointestinal disorders are idiopathic. Also, progress in this area is slow with only few new diagnostic tests having been introduced over the last decade, such as *Giardia* antigen tests, new *Clostridium perfringens* and *difficile* enterotoxin ELISAs, and a new test for diagnosis of *Trichomonas foetus* infections in cats.<sup>1-3</sup>

Examples of diagnostic tests that assess morphology are physical examination, radiology, ultrasonography, scintigraphy, and gastroduodenoscopy, which have all been available for quite some time. Newer techniques to assess morphology, such as computed tomography, magnetic resonance imaging, endoscopic ultrasonography, and endoscopic retrograde

pancreatic cholangio pancreatography (ERCP), which are used routinely for the diagnosis of human patients with gastrointestinal diseases, have only been described in a small number of small animals and are more commonly used in experimental animals rather than in veterinary patients. This lack of progress is most likely due to the limited availability of these technologies, the need for the patient and the diagnostic modality to be in the same location, and the high cost per each examination.

Examples of diagnostic tests that assess function are serum bile acids, cobalamin, folate, and trypsin-like immunoreactivity concentrations that have all been available for some time.<sup>4-8</sup> Also, there has been a lot of progress in this area and several new diagnostic tests have been introduced over the last few years, others are under investigation, and yet others are under development.

The clinical usefulness of diagnostic tests is dependent on many factors. **Sensitivity** is the number of true positive patients divided by the number of all patients with the disease and is thus a measure of how well a diagnostic test identifies patients with a disease.<sup>9</sup> **Specificity** is the number of true negative tests divided by the total number of patients without the disease and is thus a measure of how well the test distinguishes patients with the disease from those that do not have the disease.<sup>9</sup> Sensitivity and specificity are characteristic for each test and are not influenced by the prevalence of the disease.<sup>9</sup> However, for clinical practice the clinician also needs some sense of how to interpret a test result in light of the test population. **Positive predictive value** is the number of true positive test results divided by the total number of positive test results and is thus a measure for the confidence the clinician can place into a positive test result.<sup>9</sup> The **negative predictive value** is the number of true negative test results divided by the total number of test results and is thus a measure of how confident the clinician can be to exclude the disease in a patient with a negative test result.<sup>9</sup> The following example illustrates how important this information is.

Let's assume that a new diagnostic test for exocrine pancreatic insufficiency has a sensitivity of 90% and a specificity of 90%. The prevalence of the disease in the test population is 10%. A diagnostic test with those characteristics would have a positive predictive value of 50% and a negative predictive value of 99%. This would mean that while almost all dogs that have a negative test are truly negative, 50% of dogs with a positive test actually do not have the disease. Therefore, while a specificity of 90% appears rather high the positive predictive value of 50% is rather low, due to the low prevalence of the disease. Thus in order for a diagnostic test to be clinically useful the specificity needs to be higher the lower the prevalence of the disease is.

Finally, while some diagnostic tests are either negative or positive, most diagnostic tests will yield a quantitative result that needs to be interpreted. This is achieved by comparison of the result found in a diseased animal to that found in a healthy animal (reference, control, or normal

**Table.** This table shows examples of diagnostic tests for gastrointestinal disorders in dogs and cats divided into tests that assess the presence of an etiologic factor, tests that assess morphology, and those that assess function

DIAGNOSTIC TESTS			
	Etiologic Tests	Morphologic Tests	Function Tests
Diagnostic tests that are widely available	<ul style="list-style-type: none"> <li>fecal smear</li> <li>fecal floatation</li> <li><i>Parvovirus</i> antigen test</li> <li>fecal culture for specific pathogenic organisms</li> </ul>	<ul style="list-style-type: none"> <li>physical examination</li> <li>radiography</li> <li>histopathology</li> </ul>	<ul style="list-style-type: none"> <li>serum bile acids</li> <li>serum TLI</li> <li>serum cobalamin</li> <li>serum folate</li> </ul>
Diagnostic tests with limited availability	<ul style="list-style-type: none"> <li><i>Trichomonas</i> culture pouch</li> </ul>	<ul style="list-style-type: none"> <li>abdominal ultrasound</li> <li>endoscopy</li> <li>laparoscopy</li> </ul>	<ul style="list-style-type: none"> <li>serum PLI</li> <li>fecal <math>\alpha_1</math>-proteinase inhibitor</li> <li>serum C-reactive protein</li> <li><math>^{51}\text{Cr}</math>-EDTA</li> </ul>
Diagnostic tests under clinical investigation	<ul style="list-style-type: none"> <li><i>Giardia</i> antigen tests</li> <li><i>Clostridium spp.</i> enterotoxin tests</li> </ul>	<ul style="list-style-type: none"> <li>computed tomography</li> <li>magnetic resonance imaging</li> <li>echoendoscopy</li> <li>ERCP</li> </ul>	<ul style="list-style-type: none"> <li>hydrogen breath</li> <li>serum unconjugated bile acids</li> <li>intestinal permeability and mucosal function testing</li> <li><math>^{13}\text{C}</math>-aminopyrine demethylation blood test</li> </ul>
Diagnostic tests under development	<ul style="list-style-type: none"> <li>genetic markers for gastrointestinal disease</li> </ul>		<ul style="list-style-type: none"> <li>fecal and serum markers for gastrointestinal inflammation</li> </ul>

range). However, a result outside the reference range does not necessarily indicate disease and cut-off values need to be determined that afford the best test characteristics for the diagnosis of a disease. For example, if the reference range for serum ALT activity in dogs is 0–40 U/L, a serum ALT activity of 42 U/L is not enough to diagnose hepatic disease. A cut-off value must be identified that determines an abnormality significant enough to warrant diagnosis of a disease.

The following discussion is limited to examples of diagnostic tests that are aimed at assessing gastrointestinal function (Table).

## FUNCTION TESTS THAT ARE ROUTINELY AVAILABLE

### Serum Bile Acid Concentrations

Bile acids are metabolites that are derived from cholesterol degradation.<sup>10</sup> Bile acids are formed and conjugated in the liver and secreted in the bile.<sup>10</sup> After a meal cholecystokinin stimulates gall bladder contraction and release of bile into the duodenum. Conjugated bile acids play a crucial role in fat absorption as they help to emulsify fat.<sup>11</sup> A small amount of bile acids are deconjugated by the small intestinal microflora. These unconjugated bile acids are absorbed in the small intestine and are no longer available for fat emulsification. In contrast, conjugated bile acids are absorbed in the large intestine, reach the vascular space, and are extracted from the portal blood by the liver.<sup>10</sup>

Pre- and postprandial bile acid concentrations are used for the diagnosis of hepatic impairment and portosystemic shunting.<sup>4,5,12</sup> Food is withheld from the patient for 12 hours and a serum sample is collected. A small amount of food, rich in fat, is fed to stimulate gall bladder contraction and another serum sample is collected 2 hours later.

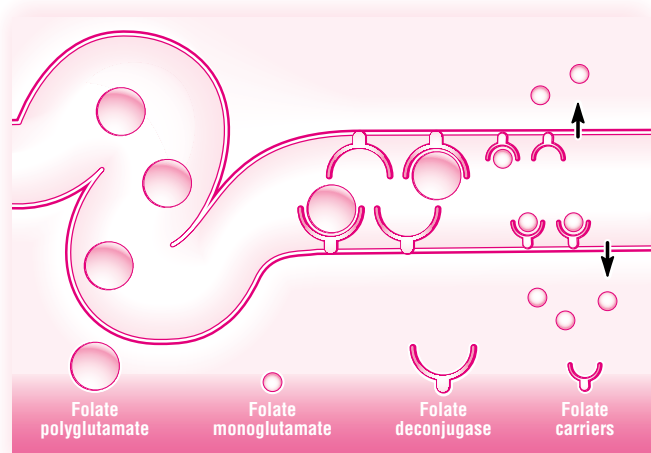
When hepatic function is significantly impaired extraction of bile acids from the portal blood becomes less efficient and both pre- and post-prandial serum bile acid concentrations increase.<sup>13</sup> In patients with portosystemic vascular anomalies pre-prandial bile acid concentrations may be only slightly increased, while post-prandial serum bile acid concentrations are often severely increased.<sup>13</sup> In some normal patients paradoxical results are observed in that pre-prandial bile acid concentrations are higher than post-prandial concentrations. It has been speculated that this finding is due to gall bladder contraction without food intake. Recently, increased pre-prandial bile acid concentrations have also been found in dogs with evidence of an altered small intestinal microflora.

Recently, the use of sulfated and non-sulfated urinary bile acid concentrations in dogs and cats with suspected hepatic disease has been described.<sup>14,15</sup> However, further studies are necessary before replacement for serum bile acid concentrations can be recommended.

### Serum Folate Concentration

Folate, a B vitamin, is a water-soluble vitamin that is plentiful in most commercial pet foods.<sup>16</sup> However, dietary folate is supplied as folate polyglutamate, which cannot be

readily absorbed. In the proximal small intestine folate polyglutamate is deconjugated by folate deconjugase and folate monoglutamate is absorbed by specific folate carriers in the proximal small intestine (**Figure 1**).



**Figure 1.** Principles of folate absorption.

During severe proximal small intestinal disease folate polyglutamate is no longer deconjugated or folate monoglutamate is no longer absorbed, leading to folate malabsorption and if the condition continues for a significant period of time folate body stores are depleted and serum folate concentration decreases.<sup>6</sup> The same is true if the patient has diffuse small intestinal disease as long as the proximal small intestine is involved. A decreased serum folate concentration occurs in a significant portion of dogs and cats with chronic small intestinal disease. Folate deficiency does not appear to lead to overt clinical signs and does not lead to further folate malabsorption. Thus folate supplementation is usually not required and serum folate concentration returns to normal after treatment of the underlying disease process.

Dogs with small intestinal bacterial overgrowth, a condition that is characterized by an altered microflora or increased numbers of microbial agents in the small intestine, may have an increased serum folate concentration as many bacterial species synthesize folic acid that is available for absorption.<sup>17</sup>

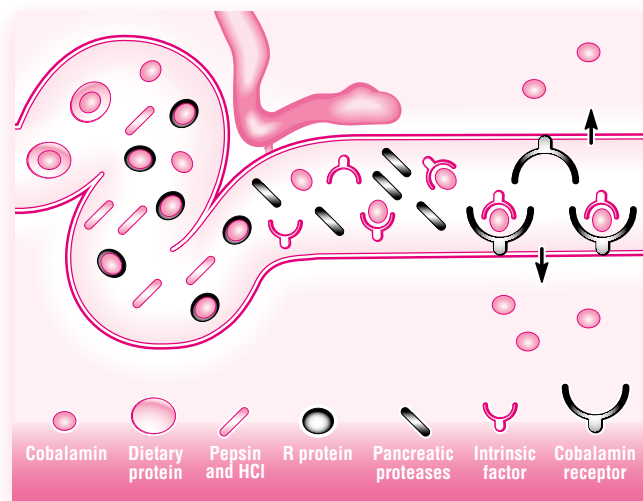
### Serum Cobalamin Concentration

Cobalamin, vitamin B12, is also a water-soluble vitamin that is plentiful in most commercial pet foods.<sup>16</sup> Dietary cobalamin is bound to dietary protein and cannot be absorbed in this form. In the stomach dietary protein is digested by pepsin and HCl and cobalamin is being released (**Figure 2**). The free cobalamin is immediately bound by R-protein (also known as haptocorrin). R-protein is mostly secreted in gastric secretions and saliva. Cobalamin bound to R-protein is once again unavailable for absorption. In the small intestine R-protein is being digested by pancreatic proteases and the released cobalamin is bound by intrinsic factor

(**Figure 2**). In dogs 90% and in cats 99% of intrinsic factor is secreted by the exocrine pancreas.<sup>18</sup> This is different from human beings where a larger portion of intrinsic factor is secreted by the stomach. Intrinsic factor cobalamin complexes are absorbed by specific receptors in the ileum (also known as cubilin; **Figure 2**).

Distal small intestinal disease, if severe enough, will lead to the destruction of cobalamin receptors in the ileum and will lead to cobalamin malabsorption.<sup>6</sup> In a recent study 61% of 80 cats with clinical signs of chronic gastrointestinal disease had a decreased serum cobalamin concentration.<sup>19</sup> Also, these cats were shown to have a shorter half-life for cobalamin compared to normal cats.<sup>19</sup> Diffuse small intestinal disease also can lead to cobalamin malabsorption as long as the ileum is involved in the disease process. Also, exocrine pancreatic insufficiency can lead to cobalamin deficiency in the dog and almost invariably does so in cats since most of the intrinsic factor is synthesized by the exocrine pancreas in this species.<sup>18,20</sup> Small intestinal bacterial overgrowth (SIBO) in dogs can also lead to cobalamin malabsorption as many bacterial species compete with the body for dietary cobalamin.<sup>17</sup> Cobalamin malabsorption in itself does not lead to cobalamin deficiency. Only if cobalamin malabsorption is long-standing do cobalamin stores of the body get depleted, ultimately leading to cobalamin deficiency.

Cobalamin is essential for many biochemical reactions in the body and virtually all tissues need cobalamin for proper function, which is reflected in important metabolic changes that occur due to cobalamin deficiency.<sup>21,22</sup> Clinical signs of cobalamin deficiency can vary. Some patients may just show lethargy, anorexia, and weight loss, while others may show diarrhea, intermittent septic episodes, or even neurological signs.<sup>23-26</sup> Experimental cobalamin deficiency in cats leads to progressive anorexia, weight loss, and an unkempt hair coat.<sup>27</sup> Additionally, human beings with cobalamin deficiency have been shown to develop



**Figure 2.** Principles of cobalamin absorption.

intestinal abnormalities such as villous atrophy, infiltration of the intestinal mucosa with inflammatory cells, further cobalamin malabsorption, and malabsorption of other nutrients.<sup>28</sup> Similar gastrointestinal signs have not been proven in dogs or cats with cobalamin deficiency but there is empirical evidence that they occur.

Canine and feline patients with chronic small intestinal disease or exocrine pancreatic insufficiency and concurrent cobalamin deficiency may not respond to therapy unless they are also supplemented with cobalamin.

### **Serum Trypsin-like Immunoreactivity Concentration (TLI)**

Pancreatic acinar cells synthesize and secrete trypsinogen, an inactive pre-form of the proteolytic enzyme trypsin. Almost all trypsinogen is released into the duct system and is released into the duodenum. However, a small amount of trypsinogen is also released into the vascular space and can be measured by use of species-specific immunoassays for measurement of trypsin-like immunoreactivity (TLI).<sup>8,29</sup>

Dogs and cats with exocrine pancreatic insufficiency have a lack of pancreatic acinar cells and thus a decreased secretion of pancreatic enzymes into the duodenum. At the same time, the amount of trypsinogen released into the vascular space is also decreased leading to a decreased serum TLI concentration. A canine TLI concentration of  $\leq 2.5$   $\mu\text{g/L}$  has been shown to be highly sensitive and specific for exocrine pancreatic insufficiency in the dog.<sup>7</sup> In cats a serum feline TLI concentration  $\leq 8$   $\mu\text{g/L}$  has been shown to be highly specific for EPI.<sup>30</sup>

Pancreatic inflammation can lead to an increased release of trypsinogen into the vascular space. Also, trypsinogen is prematurely activated and can circulate in the vascular space, though active trypsin is quickly removed by protease inhibitors. Like trypsinogen, trypsin is also detected by immunoassays for TLI and serum TLI concentration can be increased in dogs and cats with pancreatitis.<sup>31-33</sup> A significantly increased serum TLI concentration ( $> 50$   $\mu\text{g/L}$  in dogs and  $> 100$   $\mu\text{g/L}$  in cats) is highly specific for pancreatitis but has a limited sensitivity of 30–60%.<sup>34-37</sup> Serum cTLI concentration is of little clinical use for the diagnosis of canine pancreatitis as superior diagnostic tests are available for the dog. In cats, serum fTLI concentration used to be the most accurate diagnostic test for pancreatitis available, but serum fPLI concentration (see below) appears to be superior and will likely replace serum fTLI determination as more clinical experience is gained with this new assay.

## **FUNCTION TESTS WITH LIMITED AVAILABILITY**

### **Serum Pancreatic Lipase Immunoreactivity Concentration (PLI)**

Many different cell types in the body synthesize and secrete lipases.<sup>38</sup> All of these lipases have the same function,

the hydrolysis of non-polar lipids into more polar hydrolysis products, but different lipases may differ significantly in molecular structure.<sup>38</sup> Depending on the substrate and reaction conditions of the specific lipase activity assay used, any lipase reaching the vascular space may contribute to some degree to the lipase activity that is being measured when evaluating serum lipase activity. In contrast, the use of immunoassays does allow for the specific measurement of lipase originated from the exocrine pancreas.<sup>39,40</sup> Immunoassays for the measurement of serum concentrations of canine and feline pancreatic lipase have recently been developed and validated.<sup>39,40</sup>

In order to show the specificity for exocrine pancreatic function, serum cPLI was measured in a group of dogs with exocrine pancreatic insufficiency.<sup>41</sup> The median serum cPLI concentration was significantly decreased compared to clinically healthy dogs. In addition serum cPLI concentration was non-detectable in most of the dogs and minimal serum cPLI concentrations were observed in the rest of the dogs, indicating that serum cPLI concentration originates from the exocrine pancreas and is specific for exocrine pancreatic function.<sup>41</sup>

In another study serum cPLI was evaluated in dogs with experimentally induced chronic renal failure.<sup>42</sup> While serum cPLI was significantly higher in dogs with experimentally induced chronic renal failure than in clinically healthy dogs, most dogs had serum cPLI concentrations within the reference range and none of the dogs had serum cPLI concentrations that were above the currently recommended cut-off value for pancreatitis.<sup>42</sup> These data would suggest that serum cPLI concentration can be used as a diagnostic test for pancreatitis even in dogs with renal failure.<sup>42</sup>

Serum cPLI has also been evaluated in dogs with biopsy-proven gastritis.<sup>38</sup> Unfortunately, pancreatic biopsies from these dogs were not available. Of 25 dogs only 1 dog had a serum cPLI concentration above the current cut-off value for pancreatitis.<sup>38</sup> Keeping in mind the similar etiology and clinical presentation of dogs with gastritis and those with pancreatitis and also the lack of pancreatic biopsies, it appears reasonable to assume that the dog with the high serum cPLI concentration had both gastritis and concurrent pancreatitis; but this is merely speculative. Even if one assumes that this dog represents a false positive the specificity of serum cPLI concentration in dogs with gastritis is 96%. Also, long-term oral administration of prednisone did not have any effect on serum cPLI concentration.<sup>43</sup>

Finally, the sensitivity of different minimally-invasive diagnostic tests was compared in dogs with biopsy-proven pancreatitis.<sup>44</sup> The sensitivity of serum TLI concentration was below 35% and that of serum lipase activity was less than 55%.<sup>44</sup> In contrast, the sensitivity for serum cPLI concentration for pancreatitis was above 80%.<sup>44</sup>

Initial clinical studies in cats have also been promising. In a group of cats with experimentally induced pancreatitis both serum fTLI and fPLI concentrations did increase ini-

tially but serum fPLI concentrations stayed elevated much longer than did serum fTLI concentrations suggesting that, as in the dog, serum PLI concentration is much more sensitive for pancreatitis than serum TLI concentration.<sup>45</sup> In another study of cats with spontaneous pancreatitis, serum fPLI concentration was more sensitive and more specific than serum fTLI concentration or abdominal ultrasonography.<sup>46</sup>

Thus, in both dogs and cats serum PLI concentration is the most sensitive and specific diagnostic test for pancreatitis currently available. Currently, these assays are only available through the Gastrointestinal Laboratory at Texas A&M University ([www.cvm.tamu.edu/gilab](http://www.cvm.tamu.edu/gilab)). However, more universally available in-clinic tests for cPLI and fPLI are in preparation.

### **Fecal $\alpha_1$ -proteinase Inhibitor Concentration**

Many gastrointestinal disorders are associated with protein loss. Also, gastrointestinal protein loss can be used as a diagnostic marker for gastrointestinal disease when GI disease is suspected in patients that do not display overt signs of gastrointestinal disease. The gold standard for the diagnosis of gastrointestinal disease is <sup>51</sup>Cr-albumin but this diagnostic test is labor and time intensive and is also associated with exposure of the patient to radioactivity.<sup>47,48</sup> Recently, an assay for the measurement of canine  $\alpha_1$ -proteinase inhibitor in feces has been developed.<sup>49</sup> Alpha<sub>1</sub>-proteinase inhibitor ( $\alpha_1$ -PI) is synthesized in the liver and inhibits a variety of different proteins, most importantly elastase, but also trypsin, and others.<sup>50</sup> Alpha<sub>1</sub>-proteinase inhibitor has a molecular mass of approximately 60,000 Da, which is similar to albumin. Thus, when gastrointestinal disease is severe enough to be associated with gastrointestinal albumin loss,  $\alpha_1$ -PI is lost as well. In contrast to albumin,  $\alpha_1$ -PI is not hydrolyzed in the gastrointestinal tract. This is due to the fact that  $\alpha_1$ -PI is a proteinase inhibitor. Therefore,  $\alpha_1$ -PI can be measured by use of a species-specific immunoassay in feces. Dogs with gastrointestinal protein loss have an increased fecal  $\alpha_1$ -PI concentration.<sup>51</sup>

Dogs presented for hypoalbuminemia should first be evaluated for potential blood loss. After blood loss has been ruled out protein losing nephropathy and hepatic failure should be ruled out by evaluating a urine protein/creatinine ratio and serum bile acids concentrations, respectively. If all of these tests are negative measurement of fecal  $\alpha_1$ -PI can be used to confirm gastrointestinal protein loss. In addition, fecal  $\alpha_1$ -PI can be used to objectively monitor the severity of gastrointestinal disease. Finally, fecal  $\alpha_1$ -PI can be used as an early indicator of gastrointestinal disease in dogs with a family history.<sup>52</sup> For example, Soft-Coated Wheaten Terriers with protein losing enteropathy have increased fecal  $\alpha_1$ -PI concentrations long before they develop clinical signs of gastrointestinal disease or hypoalbuminemia.<sup>52</sup>

An assay for the measurement of  $\alpha_1$ -PI in cat feces is currently being validated.

### **Serum C-reactive Protein Concentration**

C-reactive protein is an acute phase reactant, a group of proteins that are synthesized and secreted by the body during inflammatory conditions.<sup>53</sup> For example, C-reactive protein is found in serum of human patients with coronary heart disease and is used as an early diagnostic marker for coronary heart disease.<sup>54</sup>

Recently, an assay for the measurement of canine C-reactive protein in serum has been developed and is commercially available.<sup>55,56</sup> Initial data has shown that serum C-reactive protein concentration correlates with disease severity of canine inflammatory bowel disease.<sup>57</sup> Thus, C-reactive protein can be used to objectively monitor therapeutic success in patients with inflammatory bowel disease. Unfortunately, measurement of canine C-reactive protein is rather expensive and is currently not widely available.

## **FUNCTION TESTS UNDER INVESTIGATION**

### **Serum Unconjugated Bile Acids**

As mentioned previously, bile acids are generated and conjugated in the liver. After release into the small intestine they are needed for fat emulsification. A small amount of bile acids gets deconjugated by bile salt hydrolase producing bacteria. The increased bacterial load in the small intestine during small intestinal bacterial overgrowth leads to increased deconjugation of bile acids. These bile acids are quickly reabsorbed and can be quantified. In a preliminary study 9 of 10 dogs with culture proven SIBO had increased serum concentrations of unconjugated cholic acid, the most prominent unconjugated bile acid in dogs.<sup>58</sup> Unfortunately, unconjugated serum bile acid concentrations are highly variable in normal dogs and this test is probably more useful for longitudinal studies rather than for the diagnosis of SIBO in clinical practice.<sup>59</sup>

### **Hydrogen Breath**

Mammalian cells do not synthesize hydrogen, but bacterial metabolism leads to the production of hydrogen. For hydrogen breath testing dogs receive a sugar solution and breath hydrogen is evaluated every 15 minutes for several hours. In normal dogs the carbohydrates of the test solution are being digested and absorbed before they reach the bacterial flora of the large intestine and only small amounts of hydrogen are being produced. However, in dogs with SIBO the carbohydrates are being fermented by the large number of bacteria in the small intestine. The hydrogen that is being released diffuses into the blood stream, reaches the alveoli, and is excreted in the expiratory air. Because the hydrogen is produced in the small intestine the peak in breath hydrogen concentration occurs early. This is in contrast to animals with malabsorption. In these patients the carbohydrates reach the bacteria in the large intestine leading

to a late peak in breath hydrogen concentration.<sup>60</sup> Further studies of the clinical usefulness of hydrogen breath testing in small animal gastroenterology are needed and in progress.

## Intestinal Permeability and Mucosal Function Testing

The intestinal mucosa serves as a barrier against uncontrolled entry of unwanted molecules that are potentially harmful to the body.<sup>61</sup> The barrier is not complete and trace amounts of a wide range of relatively small molecules can traverse the intestinal mucosa in normal animals. The integrity of the barrier function of the gastrointestinal tract has been evaluated by permeability testing in different species and the use of many different marker molecules, including <sup>51</sup>Cr-EDTA, polyethylene glycol, and mono- and disaccharides has been evaluated.<sup>62-66</sup>

In general, the gastrointestinal mucosa is believed to have two types of aqueous pores allowing non-carrier-mediated uptake of small molecules. The smaller pores are hypothesized to be located within the cell walls and are believed to allow permeation by small molecules, including monosaccharides.<sup>67,68</sup> The overall frequency of these transcellular pores is believed to be quite large and mostly dependent on the total surface area of the intestinal mucosa. Small intestinal disease is often associated with a decrease in surface area leading to a decrease of intestinal permeability to monosaccharide markers.<sup>69</sup> The larger pores with a maximal radius ranging from approximately 0.5 to 0.8 nm are believed to be located paracellularly in the area of the tight junctions.<sup>67,69,70</sup> The overall frequency of these pores, which allows permeation of larger molecules such as <sup>51</sup>Cr-EDTA and disaccharides, is much smaller and is largely dependent on mucosal integrity.<sup>66,70</sup> During many small intestinal disorders tight junctions become more leaky leading to increased permeation of disaccharide markers.<sup>69</sup>

Recently, sucrose has been used as a specific marker molecule to evaluate permeability of the gastric mucosa.<sup>71-74</sup> The urinary recovery of other monosaccharides transported across the intestinal mucosa by specialized carriers, such as methylglucose and xylose has also been used to evaluate small intestinal absorptive capacity, thereby concurrently evaluating another aspect of small intestinal mucosal function.<sup>65,75-77</sup>

For gastrointestinal permeability and mucosal function testing, a sugar solution is administered by orogastric intubation; the sugars permeate the gastroin-

testinal mucosa or are absorbed by a carrier-mediated process, reach the vascular space, and are quantitatively evaluated in serum or in the urine.<sup>78,79</sup>

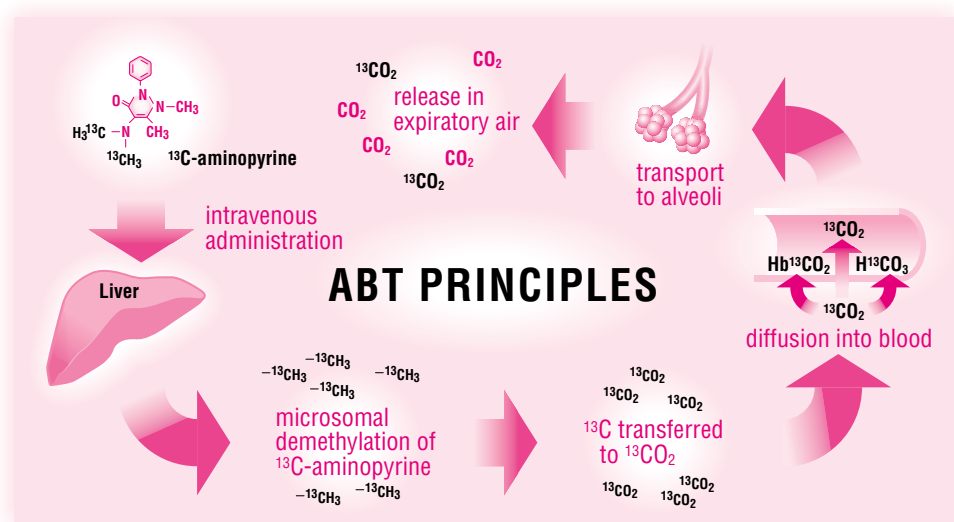
Gastrointestinal permeability and mucosal function testing has been evaluated in many gastrointestinal diseases and even systemic diseases but a generally agreed-upon protocol for dogs and cats has not been established as of yet.<sup>80-83</sup>

## <sup>13</sup>C-aminopyrine demethylation blood test

Currently, only one clinically significant hepatic function test is available, pre- and post-prandial serum bile acid concentrations. However, this test is not very specific for loss of hepatic function.<sup>13</sup> Dogs with intra-hepatic or post-hepatic biliary obstruction have increased serum bile acid concentrations with initially unaltered hepatic function.<sup>13</sup> Other quantitative hepatic function tests that have been investigated have been shown to be of little use clinically.<sup>84</sup>

The aminopyrine breath test (ABT) has been shown to be useful in quantifying hepatic microsomal enzyme function in human beings and laboratory animals.<sup>85</sup> Several studies have shown that the ABT is a useful indicator of disease severity in human patients with chronic hepatitis or hepatic cirrhosis.<sup>86</sup>

Aminopyrine, a compound chemically similar to the nonsteroidal antiinflammatory drugs antipyrine and phenylbutazone, is demethylated by microsomal enzymes in the liver. The liberated methyl groups are oxidized to CO<sub>2</sub>, which diffuses into the blood stream, reaches the pulmonary alveoli, and is released into the expiratory air (**Figure 3**).<sup>85</sup> The administration of aminopyrine labeled with either <sup>13</sup>C or <sup>14</sup>C isotopes allows for the specific measurement of CO<sub>2</sub> derived from aminopyrine, by detection of CO<sub>2</sub> isotopes released in the expiratory air. The amount of CO<sub>2</sub> is measured as a percent dose of aminopyrine administered.



**Figure 3.** This figure shows the principle of the <sup>13</sup>C-aminopyrine breath test. <sup>13</sup>C-aminopyrine is administered to the patient. After reaching the liver aminopyrine is demethylated by microsomal enzymes and the <sup>13</sup>CH<sub>3</sub>-groups are oxidized to <sup>13</sup>CO<sub>2</sub>. The <sup>13</sup>CO<sub>2</sub> diffuses into the blood and reaches the alveoli where, together with <sup>12</sup>CO<sub>2</sub>, it is released in the expiratory air.



Reproducible collection of breath samples can be difficult in veterinary species. In addition, the handling of biological fluids from veterinary species poses a negligible infectious threat for health care professionals and laboratory staff. Therefore, a  $^{13}\text{C}$ -aminopyrine demethylation blood test has been developed and has recently been shown to be feasible in both dogs and cats. Also, the kinetics of aminopyrine demethylation has been described in clinically healthy dogs and cats. A large study is currently underway to measure  $^{13}\text{C}$ -aminopyrine demethylation in dogs and cats that undergo hepatic biopsy. Initial results have been promising.<sup>87</sup>

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# Inflammatory Bowel Disease and Pancreatitis in Cats

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## INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Diseases (IBDs) are a diverse group of intestinal disorders, which have been grouped together based on their histopathological commonalities. This is somewhat unfortunate, in that the tendency is to see “IBD” as a diagnostic endpoint, with a sole treatment protocol, rather than as a description of a pathophysiologic response. The term “IBD” should ideally be restricted to those forms in which all identifiable etiologies have been ruled out, and with good conscience, one can term the condition “idiopathic” in etiology.

“The normal intestine is usually in a steady state of physiologic inflammation, representing a dynamic balance between factors that activate the host immune system (e.g., luminal microbes, dietary antigens, endogenous inflammatory stimuli) and host defenses that maintain the integrity of the mucosa and down-regulate inflammation.” (Crawford JM.

The Gastrointestinal Tract. In: Cotran RS, Kumar V, Robbins SL, eds. *Robbins Pathologic Basis of Disease*. Philadelphia: WB Saunders Co, 1994; 755-829.) Inflammatory bowel disease seems to represent a loss of this balance.

As in humans with Crohn’s Disease, IBD primarily localized in the small bowel responds differently than disease primarily localized in the large bowel, even when the histologic lesions are similar. Unlike people, however, cats seem to respond more readily to dietary therapy. It is important to distinguish between a food hypersensitivity or food intolerance and IBD, which is, by definition, a term given to a group of disorders of unknown etiology. That is not to say, however, that IBD may not benefit from dietary therapy because the gut is naïve relative to the novel antigens. Current thought is focused on defects in the mucosal immune system as the probable cause, which initiates or perpetuates the pathophysiology underlying IBD.

There are several lines of reasoning supporting an autoimmune mechanism in IBD. These include the following:

- Lymphocytic, eosinophilic, and plasma cell infiltration occurs in tissues involved in hypersensitivity reactions.
- Resolution of disease occurs with immunosuppressive therapy. (This may, however, be an epiphenomenon reflective of the multiple effects of the drugs used.)
- Other diseases known or suspected to have an immunological basis occur concurrently in people with IBD. Similarly, in cats with IBD, nephritis, cholangiohepatitis and pancreatitis with lymphocytic-plasmacytic infiltrates are recognized commonly.
- Finally, disorders of the immune system are often multisystemic.

For normal intestinal immunity, an intact mucosal barrier is required. Because antibodies to enteric antigens are found in some people with IBD, a defect in mucosal permeability is suspected. It is not clear whether increased gut permeability occurs as a cause or a result of inflammation.

All of these disorders have inflammatory cells infiltrating the mucosa and lamina propria of the intestinal tract, sometimes, regionally, other times diffusely generalized. The infiltrate most commonly consists of lymphocytes and plasma cells, but can also be of a neutrophilic, eosinophilic or granulomatous character. The infiltrate is described by the predominant cell type present. From a pathologist’s perspective, a problem with describing the severity of the lesions is that, like describing cell populations in tracheal wash specimens, there is controversy and difference of opinions in how many cells of each type are normal in cat gut.

The result of these responses is a bowel that has regional or diffuse sections of rubbery walls thickened with edema, inflammation, and fibrosis. It is critical to verify by full thickness biopsy, whether there is evidence of intestinal lymphosarcoma as this may look similar to lymphocytic-plasmacytic IBD in the superficial luminal layers of the bowel. Chronic inflammation of the bowel may be self-perpetuating and IBD may progress to small cell lymphoma.

## History and Clinical Findings

Clinical signs vary with location of the inflammatory process: duodenal and gastric lesions usually present as vomiting and weight loss while small intestinal or colonic lesions present as diarrhea +/- weight loss (if small intestinal). However, some colonic IBD may cause vomiting as well. There are also cats in whom the inflammatory process extends beyond the gastrointestinal tract and affects the liver (+/- the gallbladder) and pancreas. This is fondly termed “triaditis” (see below). These cats may present with signs attributable to these organs, which may or may not include vomiting and diarrhea.

Most commonly, cats are presented with a history of chronic, intermittent problems, which may have been going on for weeks to years and may or may not be progressive. There is no breed or sex predilection and, although it can be diagnosed in any age cat from several months of age upward, there are more who are middle aged. Vomiting occurs acutely, may occur over a period of days and then cease till the next episode, or may occur daily. It is unrelated to eating and usually is clear froth or fluid or bile, but may include undigested/semi-digested food contents. The cat may seem otherwise completely well, or be lethargic and inappetent.

Diarrhea, if present, is of a chronic and unresponsive nature, and weight loss may be dramatic. The character of the stool varies widely, and may even be steatorrheic. If malabsorption is involved, the cat may have a voracious appetite, otherwise the history is unremarkable. Large intestinal lesions predispose to tenesmus, increased frequency of defecation +/- urgency, blood, mucous, and a change in or loss of litterbox habits. It is helpful to characterize existing diarrhea as small or large bowel in origin.

Other differentials for chronic diarrhea, weight loss, voracious appetite in cats include hyperthyroidism, lymphoma, exocrine pancreatic insufficiency and occasionally the cholangitis/cholangiohepatitis complex. Bacterial overgrowth, giardiasis and other parasites, adenocarcinoma, histoplasmosis, FIP, FeLV, and FIV are additional considerations.

Occasionally cats will be asymptomatic other than weight loss. Palpably thickened intestinal loops may be present and enlargement of the mesenteric lymph node may be noted. Mild dehydration may be evident.

## Diagnostics

A baseline CBC, biochemical profile, T4, lipase, FeLV/FIV, urinalysis, fecal exam for parasites, rectal cytology (if large intestinal diarrhea) and fecal culture and sensitivity are rational first choices.

Hematologically and biochemically there are often minimal changes: a stress leukogram is common, +/- eosinophilia, a mild non regenerative anemia, +/- hyperglycemia, mild hypoalbuminemia, hypo or hyperglobulinemia, hypokalemia, +/- mildly elevated liver enzymes.

Second tier diagnostic tests rely on indirect visualization. Radiographic and ultrasonographic findings may be unre-

markable and non-specific; nevertheless, they may be helpful from the standpoint of determining the extent of the apparent disease process and in making appropriate recommendations towards direct visualization and biopsy via endoscopy vs. exploratory laparotomy. Ultrasound will often show regional thickening of intestinal walls, which retain normal architectural layers.

Can these changes progress to more severe disease? There is evidence of biopsy proven lymphocytic-plasmacytic enteritis (LPE), relapsing as diffuse intestinal lymphoma after years of good response to therapy. It is possible that severe lymphocytic-plasmacytic IBD may be a pre cancerous lesion. It is also noteworthy, however, that partial thickness endoscopic biopsies may miss the telltale neoplastic lymphoblasts because they are found in the muscularis and deeper layers. This risk can be minimized by harvesting many good quality tissue samples from each section of the gastrointestinal tract being evaluated.

### Note:

The presence of increased inflammatory cells in an intestinal biopsy does not necessarily confirm a presumptive diagnosis of IBD. Biopsy criteria *MUST* include increased proprial lymphocytes and plasma cells, however there must also be alterations in the mucosal structure, such as villous atrophy/fusion, cryptal separation with edema, infiltrate and fibrosis. One must eliminate the other known and detectable causes of chronic inflammation first. Therefore, parasitic infestations and retroviral infections should be tested for. **A dietary trial with a limited antigen diet should be undertaken for a minimum of 6–8 weeks** and the possibilities of bacterial overgrowth or lymphoma should be considered.

If exploratory laparotomy is pursued, biopsy the stomach, duodenum, jejunum (several sites) and ileum (+/- colon). Get a definitive diagnosis wherever you can. Biopsy the liver and pancreas. Place one piece in culture medium in case a suppurative condition is found. It is helpful to differentiate between lymphocytic vs. suppurative cholangitis or cholangiohepatitis in determining an appropriate treatment protocol.

Evaluate for any and all allergens to check for or eliminate them if possible.

- Evaluate for food hypersensitivities and feed a unique antigen diet
- Deworm
- Treat for hairballs

Suppress/modulate the immune system using metronidazole (Flagyl™) to inhibit cell mediated immunity (CMI) and eliminate coexisting protozoal and anaerobic infection (10 mg/kg PO BID). If liver disease is present, reduce the metronidazole dose to 7.5 mg/kg PO BID. If dietary manipulation and metronidazole therapy are inadequate for controlling the clinical disease, addition of omega 3 fatty acids could be considered, in an attempt to interfere with arachadonic acid cascade thus reducing the inflammatory

response. However, as long as the diarrhea persists, they should be avoided, as unabsorbed fatty acids are hydroxylated by intestinal bacteria, stimulating colonic water secretion thus exacerbating diarrhea and fluid loss. Corticosteroids should be used to suppress the immune response. It is very important to start with a high dose before decreasing if they are to be used effectively! (2–4 mg/kg PO divided BID prednisone or dexamethasone 0.2 mg/kg PO BID)

### Important:

Suppress the process, so that there are **NO SIGNS** for 2 weeks before decreasing the corticosteroid dose, gradually to the lowest alternate day or once a day dose that controls the signs completely.

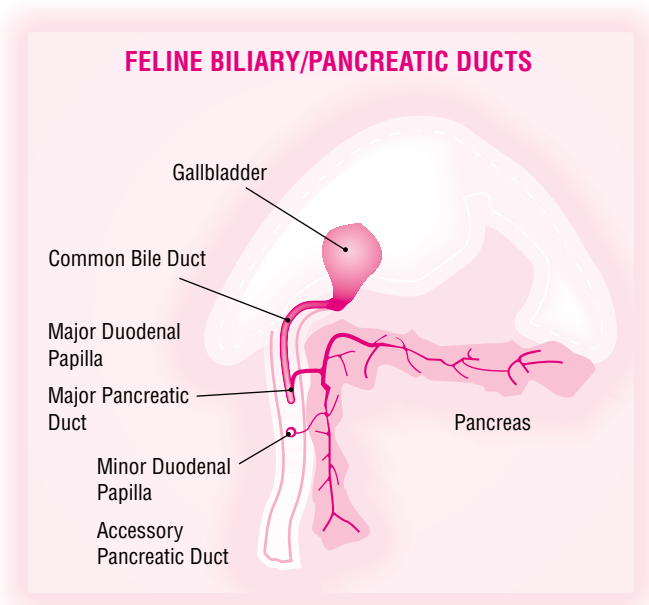
Other therapies...

- Consider antibiotics for bacterial overgrowth (tylosin [Tylan™] 10–20 mg/kg PO BID).
- Vitamin K may be indicated where severe fat malabsorption predisposes to Vit K responsive coagulopathy.
- Serum cobalamin and folate may be indicated due to intestinal malabsorption or decreased production (Folate is given orally (0.5–1.0 mg q24h X 1 month); cobalamin must be given parenterally (125–250 mcg/week SC or IM once a week X 4–6 weeks).
- Fiber-enriched diets or supplements may be helpful in chronic large bowel diarrhea to absorb excess intestinal fluid and neutralizing toxins.
- Chlorambucil (Leukeran™) 0.25–0.33 mg/kg PO q 3 days [2 mg PO q3d]
- Cytotoxic (azathioprine [Immuran™] 0.3 mg/kg PO eod) MONITOR CBC. Note also, that beneficial effects may lag 2–3 weeks behind initiation of azathioprine therapy and may be needed for 3 to 9 months.
- Cyclophosphamide (Cytosan™) 50 mg/m<sup>2</sup> orally for 4 successive days each week. Note: MONITOR CBC before next dose
- Colonic antiinflammatory (sulfasalazine [Azulfidine™], a 5-ASA-sulfa agent 0.2–0.3 mg/kg PO q 24–48 hours) Note: observe for KCS and salicylate toxicity.

### “TRIADITIS” VS. “IBD”

The term “triaditis” refers to a constellation of inflamed organs that are adjacent to each other, namely the small intestine, liver, and pancreas. Anatomically and pathologically, it is “logical” to understand why this may occur. Pathology in the distal common bile duct, either ascending from the duodenum or originating in the duct itself, (such as infection or cholelithiasis), can predispose to pancreatitis because of the functional relationship between the major pancreatic and common bile duct sphincters in the cat. Experimentally, it has been shown that when the major

pancreatic duct is perfused with bile acids, marked structural changes occur not only within the pancreatic duct, but also in the pancreas itself. (This is why feline pancreatic disease is a common cause of extrahepatic biliary obstruction.) In approximately 80% of cats, the accessory pancreatic duct is absent. The pancreatic duct enters the common bile duct before the latter opens into the duodenum at the major duodenal papilla (**Figure**).



**Figure.** Normal anatomy of the common bile duct and pancreatic duct in the cat. (Adapted from Center SA, *Diseases of the gall bladder and biliary tree* in Guilford WG (ed). *Strombeck's Small Animal Gastroenterology*, Philadelphia, WB Saunders Co, 1996, p860.)

### GASTROINTESTINAL (GI) LYMPHOMA

Lymphoma is the most common form of GI neoplasia in cats. Alimentary lymphoma has, in the past, been given a poor/grave prognosis. Dr. Keith Richter presented important findings emphasizing the need to distinguish between lymphocytic and lymphoblastic lymphomas. In a study of 67 cats, Dr. Richter found, through extensively biopsying stomach and small intestine endoscopically as well as surgically, that 90% of lymphocytic lymphoma involved the small intestine and might have been missed with endoscopy alone. For *lymphoblastic* lymphoma, approximately 50% of the cases involved small bowel only; the remainder involved stomach or stomach and small bowel. On histology, 25% of the 67 cases had *lymphoblastic*, 75% had *lymphocytic* lymphoma.

It is important to differentiate between the two types of lymphoma because they are treated very differently and because they have a different prognosis. Lymphocytic GI lymphoma is readily treated by the client in the home envi-

ronment with prednisolone (2–4 mg/kg PO divided BID) and clorambucil (2 mg PO q3days). The median disease free interval was 20.5 months (range 5.8–49 months). Rescue was achieved with cyclophosphamide. Cats with lymphoblastic lymphoma, on the other hand, responded poorly to chemotherapy using either CVP (cyclophosphamide, vincristine, prednisolone) or ACOPA (CVP + doxorubicin and L-asparaginase). Of interest also was his observation that cats with lymphoblastic lymphoma were more likely to have recurrences of abdominal masses.

## PANCREATITIS

For years, feline pancreatitis has been assumed to be a similar disease to that in dogs. Currently, as with so many other disorders, it is recognized that this group of disorders is different in the cat. Remembering that the term “pancreatitis” implies nothing more than inflammation of that organ, it is not surprising that each species may have a variety of etiologies.

The incidence of pancreatitis is higher than previously believed. In fact, in a German retrospective study, the prevalence of pathologically significant lesions in dogs was found to be 1.5% and in cats, 1.3% of the specimens submitted. Indeed, there are papers reporting the incidence as high as 2.9 and 3.5% of necropsied cats.

Drs. Jörg Steiner and David Williams classify feline pancreatitis as acute or as chronic. Acute pancreatitis is a short term, completely reversible and without fibrosis on biopsy evaluation. Chronic pancreatitis is a long-term inflammation of the pancreas associated with irreversible histopathological changes, primarily fibrosis. Most of what we see in cats is the latter which is unfortunate in that it isn't curable; however, it can generally be controlled and is less fatal than severe necrotizing pancreatitis. Diabetes mellitus may be a result of chronic pancreatitis in some individuals.

Both acute and chronic pancreatitis can be mild or severe, but most commonly acute cases tend to be more severe, and chronic cases mild. Mild pancreatitis generally results in minimal clinical signs, minimal necrosis, and low mortality.

In severe pancreatitis, (necrotizing, hemorrhagic) extensive pancreatic necrosis and multiple organ involvement +/- organ failure are seen. Fortunately, because in cats this form is rare, severe multi-system complications are uncommon. The prognosis for severe pancreatitis is poor.

Pancreatic complications may or may not be present including fluid accumulation around the pancreas, infection of necrotic areas, pseudocysts, and abscesses.

It is conceivable that we will have histopathological classification schemes in the not too distant future (eg, focal suppurative, diffuse fibrosing, lymphocytic/plasmacytic, eosinophilic pancreatitis, etc.). This should help in designing appropriate therapeutic protocols for our patients. In order to achieve this goal, pancreatic biopsies are required for histopathological evaluation in our patients.

## Etiology

1. More than 90% of the cases of feline pancreatitis are idiopathic.
2. Anything causing ischemia to the organ. “The most pivotal determinant in the development and progression of pancreatitis is likely the maintenance of local blood flow. Ischemia favours progression to an auto-digestive state; impairment of the microcirculation results in retention of activated enzymes, depletion of anti-proteolytic proteins, and reduced removal of toxic products. Necrosis of the gland follows pancreatic ischemia, leading to a self-perpetuating cycle of damage.” (Center SA, Proceedings of AAFP 2000 Fall Meeting)
3. Traumatic pancreatitis has been reported in a few cats associated with motor vehicle accidents or high-rise syndrome.
4. Several infectious agents have been implicated including feline parvovirus, *Toxoplasma* organisms (of 45 pancreata examined in 100 cats infected with *Toxoplasma*, 38 had lesions), feline herpesvirus I, *Eurytrema procyonis* (a fluke), feline infectious peritonitis (FIP), and, rarely, *Amphimerus pseudofelineus*. Look for toxoplasmosis.
5. Feline pancreatitis was reported in 2 cats following topical fenthion administration (organophosphate intoxication is a common cause of pancreatitis in children in developing countries).
6. Experimentally, hypercalcemia induced by calcium gluconate IV; and pancreatic duct infusion of oleic acids or infected fluids have induced pancreatitis in experimental models but probably are not significant causes of spontaneous pancreatitis.
7. Drugs have been implicated as causing pancreatitis in humans and dogs but not yet in cats. Drugs associated with pancreatitis in humans include azathioprine, chlorothiazide, hydrochlorothiazide, estrogens, furosemide, tetracycline, sulfonamides, L-asparaginase, 6-mercaptopurine, methyl dopa, pentamidine, nitrofurantoin, dideoxyinosine, valproic acid, and procainamide. Bear these in mind when selecting medications for patients with suspected pancreatitis.
8. NOTE. There is no evidence for glucocorticoids causing acute pancreatitis in dogs or in cats!

## Pathogenesis

It is believed that various noxious stimuli can cause the exocrine pancreas to decrease the secretion of pancreatic enzymes, followed by the formation of cytoplasmic vacuoles with the co-localization of proenzymes of digestive enzymes and lysosomal enzymes. Normally the lysosomal enzymes are strictly segregated from proenzymes to prevent premature activation of the proenzymes. A decreased pH along with the loss of segregation of the lysosomal enzymes and proenzymes cause abnormal intrapancreatic activation of trypsinogen which, when activated to trypsin, activates other proenzymes resulting in a local and systemic inflammatory response.

## Clinical Findings

Pancreatitis should be included in a diagnostic rule-out list whenever there is a history of lethargy, anorexia, dehydration, hypothermia, vomiting, abdominal pain, abdominal mass effect, dyspnea, diarrhea and ataxia. One retrospective study reported that vomiting occurred in only 35% of cats with pancreatitis. Concurrent problems may include hepatic lipidosis, cholangitis/cholangiohepatitis, idiopathic inflammatory bowel disease, enteritis, diabetes mellitus, and vitamin K1 responsive coagulopathy. As such, the clinical findings on examination may be vague.

Statistically, 38% of cats diagnosed with hepatic lipidosis had concurrent acute pancreatitis and these patients were more likely to be cachectic and have coagulation abnormalities. This is very important, as these lipidotic cats have a worse prognosis.

### Note:

The most common clinical problems in cats with pancreatitis are lethargy, anorexia, and dehydration.

## Diagnostics

The classical signs of abdominal tenderness or mass effect in the right anterior quadrant, haziness in this region and displacement of abdominal viscera on abdominal radiographs and/or visualization of a (nodular) hyperechogenicity or peripancreatic fluid or a pancreatic abscess or mass on ultrasound examination support the presumptive diagnosis of pancreatitis. However, these findings are not common.

- 1) Radiographic findings may include reduced contrast in the cranial abdomen, localized dilatation of small intestinal loops, displacement of abdominal organs with the duodenum often moved dorsally and laterally, the stomach moved to the left, and the transverse colon caudally.
- 2) Ultrasonographic findings may include the following changes in the pancreas: swelling, increased echogenicity of the pancreas and peripancreatic fat, mass effects, and fluid accumulation around the pancreas.
- 3) Contrast-enhanced computed tomography (CT) is used in humans to diagnose and stage the severity of pancreatitis with its ability to detect and delineate areas of necrosis.

Practically speaking, ultrasound is the most sensitive, commonly available, non-invasive evaluative tool that we have at this time.

Biochemically and hematologically, changes are most commonly mild and nonspecific. There may be a mild, non-regenerative anemia in chronic pancreatitis or a severe

anemia terminally in acute, necrotizing pancreatitis. An inflammatory or stress leukon may be present, and in the case of a pancreatic abscess or a suppurative pancreatitis, a left shift may be seen.

Concurrent elevations of sap and alt are not uncommon and reflect inflammatory or lipidotic involvement of the liver. Nonspecific changes, such as hyperglycemia (stress or concurrent diabetes), hypocalcemia, hypokalemia (inappetance), hypercholesterolemia, azotemia (prerenal and/or renal), and hyperbilirubinemia have all been reported.

The lack of sensitivity and specificity of amylase and lipase is a source of frustration in diagnosing feline pancreatitis. Elevations in serum amylase may occur not only with pancreatitis, but more commonly from other gastrointestinal diseases, as well as from decreased renal clearance of this enzyme. Additionally, a normal serum lipase cannot be depended on to rule-out pancreatitis.

Trypsin-like immunoreactivity (TLI) has been shown to be diagnostic for severe acute pancreatitis. However, it does *not* detect the more common, chronic and milder forms of pancreatitis. Trypsinogen and trypsin are pancreas-specific in origin, and both are detected by the TLI assay. Serum TLI is very specific but *not* sensitive. Even though published normals are 17–48 micrograms/dl values under 150–200 are equivocal (GI Laboratory at Texas A&M University). TLI seems most reliable in identifying acute pancreatitis. Later in the course of disease it may not be elevated either because the sick pancreas has leaked all of the enzymes that it had made and is not capable of producing more (after several days of inflammation) or the pancreatic blood flow has decreased following the worst phase of the inflammatory response.

Recently, feline pancreatic lipase immunoreactivity has been validated by the GI Laboratory at Texas A&M University. In an abstract presented at the ACVIM Forum 2003, Dr. MA Forman showed that “feline PLI and abdominal ultrasound have good sensitivity and specificity, whereas helical CT does not appear to be a useful screening tool for the diagnosis of feline pancreatitis.”

The same group looked at serum and urinary markers for feline pancreatitis and found that: “both serum fTLI and trypsinogen activation peptide (TAP) concentrations were significantly higher in cats with pancreatitis than in clinically healthy cats...(whereas) urine TAP and urinary TAP/creatinine ratio do not appear to be clinically useful for diagnosing feline pancreatitis.”

Ultimately, surgical biopsy is required to make a definitive diagnosis. Whilst dogma was that biopsying the pancreas is a pathophysiologically dangerous undertaking, this does not appear to be the case in the cat. The author routinely biopsies pancreatae in all of her exploratory patients.

The procedure is simple: gently isolate the pancreas from the surrounding viscera and pack it off with a few gauze swabs prior to selecting either a gross lesion or routine selection of

both poles for biopsy using fine iris scissors. Submit a small piece in culture medium as well as formalin preserved samples, in case the lesion is reported as suppurative. Biopsies may also be collected via laparoscopy.

## Therapy

Therapy for pancreatitis is best planned with knowledge of the type of pancreatitis present. Fluid therapy, pain relief, and nutrition are the cornerstones in supportive care. The goals of fluid therapy are to sustain blood and plasma volume, normalize blood pressure, and to correct acid-base and electrolyte disorders. Concurrent problems (such as lipidosis or enteritis) should be addressed as well. A noteworthy difference between the dog and cat is the recommendation to feed, rather than fast, those patients suspected of (or confirmed as) having pancreatitis unless they are vomiting. Even with the vomiting cat, designing a nutritionally supportive protocol is of great importance due to this species' predisposition for developing lipidosis. It is important not to fast cats for longer than 48 hours. Utilize anti-emetics as necessary. In the rare case where vomiting cannot be controlled even with ondansetron, total parenteral nutrition or jejunostomy tube feeding may be advisable for 7–10 days. Discussion of tube feeding (nasogastric, esophageal, gastrostomy, jejunostomy) is beyond the scope of this article.

If concurrent liver pathology is present, drug doses, including anti-emetic agents, should be reduced to take the impaired hepatic metabolism into consideration. Anti-emetics commonly used in the cat include metaclopramide (Reglan™) and chlorpromazine (Largactil™). Each of these drugs also has its own, inherent side effects, such as the central nervous system (CNS) sedation or frenzied behavior or disorientation of Reglan™ in the cat or the hypotensive effect of the Largactil™. Other antiemetics should be considered (**Table**). Zofran™ while costly, is very beneficial in the intractably vomiting patient.

It has been suggested that bland, low-fat, high-carbohydrate diets are most suitable; however, this author is not aware of any research done supporting this recommendation. Cats, being obligate carnivores, do not normally utilize carbohydrates well, therefore feeding a balanced, non protein-restricted diet is warranted. Restriction of fat is not indicated.

Modification of gastric acidity is advised; the gastric pH can be checked by measuring pH of vomitus or by gastric suctioning via a nasogastric (or other) tube. An H2 blocker, such as famotidine (0.5 mg/kg IV q12h) or a proton pump inhibitor, such as omeprazole (0.5–1.0 mg/kg PO q24h) may be used.

While pancreatic enzymes are generally only used in feline exocrine pancreatic insufficiency, David Williams has mentioned their use in human pancreatitis patients to reduce pain through feedback to the pancreas inhibiting further enzyme release (and leakage). Whether this is of benefit in cats (or dogs) is not known.

Analgesia is of critical importance in the comfort of the patient, but also in the progression of the disease/inflammation through the negative physiological effects of pain. **Pain causes disease and prevents healing.** Even if obvious abdominal pain isn't present, a test dose of 0.1–0.2 mg/kg oxymorphone IV, to see if the patient improves over the approximately 6-hour effective period, should be offered. If improvement is seen, then constant rate infusion of a narcotic may be considered or a transdermal fentanyl patch (Duragesic™) for continuous relief. Torbugesic™ is not as effective for visceral pain as the mu opioid agonists are. (A thorough discussion of analgesia is beyond the scope of this paper.)

Antibiotics are only indicated if the diagnosis of a suppurative pancreatitis has been made. In this case, antimicrobial selection is best made with the knowledge of a sensitivity spectrum. Generally gram negative and anaerobic organisms are implicated. Note that a suppurative pattern may be seen on histology in a *sterile* pancreatitis caused by enzyme damage.

Corticosteroids are indicated if a lymphocytic/plasmacytic form is reported or in an acute shock presentation. Other anti-inflammatories are not currently recommended; nor have any benefits been seen with the use of antacids, anticholinergics, GI hormones (somatostatin, glucagon), or calcitonin. Dopamine has been useful in acute experimental feline pancreatitis.

Fresh frozen plasma may be considered in cats with severe pancreatitis to replace plasma proteases, albumin and alpha 2 macroglobulins. Selenium was shown to be useful in dogs, however, to date; no study has been done to assess the role of selenium in therapy of pancreatitis in cats.

**Table.**

### SELECT ANTI-EMETICS FOR USE IN THE CAT

Generic Name	Product™	Dose (feline)
Chlorpromazine	Thorazine, Largactil	0.5 mg/kg q8h IM
Prochlorpromazine	Compazine	0.1 mg/kg q6h IM
Diphenhydramine	Benadryl	2.0-4.0 mg/kg q8h PO 2.0 mg/kg q8h IM
Dimenhydrinate	Dramamine	8.0 mg/kg q8h PO
Prochlorpromazine + Isopropamide	Darbazine	0.5-0.8-mg/kg q12h IM, SQ
Metoclopramide	Reglan	1-2 mg/kg constant rate infusion IV over 24 hours
Ondansetron	Zofran	0.1-0.15 mg/kg slow push IV q6-12 hours prn
Dolasetron	Anzemet	0.6 mg/kg IV q24h



Complications of ACUTE pancreatitis that may arise include DIC, thromboembolism, cardiac arrhythmia, sepsis, acute tubular necrosis, pulmonary edema, and pleural effusion. It has been suggested that a low dose of dopamine (5 mcg/kg/min) diminishes the severity of the disease. To prevent bacterial translocation, cover these patients with broad-spectrum antibiotics.

## Prognosis

The prognosis for cats with pancreatitis depends on the type of pancreatitis as well as the degree of duration and severity. Many cats have chronic, low-grade smoldering pancreatitis and live long lives, but will have a better quality of life if a definitive diagnosis is made resulting in appropriate therapy.

## SUGGESTED READING

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# Dietary Management of Gastrointestinal Issues and Obesity in Dogs and Cats: Clinical Studies

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## INTRODUCTION

Gastrointestinal issues are a top five complaint among pet owners and are a top reason for presentation of dogs and cats to veterinarians, accounting for between 20 and 25% of veterinary visits.<sup>1,2</sup> Among cat owners the top digestive-related health complaint has been reported as production of hairballs. Cat owners cited cleaning up after their cat and maintaining their cat's health as the greatest challenges in cat ownership.<sup>1</sup> Problems with hairballs likely play into each of these challenges of cat ownership. Diet has been proposed as a way to reduce the incidence of hairballs in cats. A recently completed clinical study (discussed below) demonstrates the benefit of a moderate addition of fiber to the diet in reducing hairball frequency.<sup>3</sup>

Stress can be a trigger of gastrointestinal upset resulting in diarrhea. For example, the stress of boarding can be a trigger for this situation. Dietary management can have an important role in managing stress-related diarrhea in dogs as illustrated in the second study outlined below.

Obesity is considered to be the most common nutrition-related condition in companion animals. In dogs the incidence of obesity has been estimated to be 25 to 30%.<sup>4,5</sup> Although dogs are not typically presented to veterinarians with the complaint of obesity, they are presented for conditions that may be predisposed to by obesity, such as diabetes, or that are exacerbated by obesity, such as hip dysplasia. The standing recommendation is to reduce weight in these dogs—but what is the documented benefit? This is the central question examined in the third study on the effect of weight loss on hip osteoarthritis.<sup>6</sup>

## DIETARY MANAGEMENT OF HAIRBALLS

Diet has been suggested as a way to help reduce the frequency of hairballs in cats. To determine the impact of diet in managing hairballs, cat owners were screened for participation in an in-home clinical study. Owners with indoor-only cats observing one or more hairballs per cat per month were eligible for the study. Cats requiring special or prescription diets were excluded from the study.

Participants were blinded to the identity of the study diets. Cats were fed Iams Original™ for a one-month baseline period. The cats were then randomized to a crossover design in which cats were fed Iams Original™ or Iams Hairball Care™ for two months each. The essential difference between the two diets is the addition of cellulose as a fiber source in the Iams Hairball Care™ (*Table 1*).

**Table 1.**

### HAIRBALL STUDY DIET COMPOSITION

	Iams Original™	Iams Hairball Care™
Protein, %	35.5	36.4
Ash, %	6.5	6.7
Crude Fiber, %	1.9	5.0
Fat, %	24.8	22.7
ME (Kcal/kg)	4483	4234

Owners recorded the observed occurrences of hairballs and vomiting for each study period on a calendar. An incident was considered to be a hairball if hair made up a majority of the emission; if hair was absent or a minor component of an emission it was considered an occurrence of vomiting. There were 102 cats from 47 households that completed all three phases of the study. Owners were not always able to distinguish which cat produced a given hair-

ball, therefore results for hairball and vomiting frequency were analyzed on a household basis. Owners completed a questionnaire at the end of the study regarding their experience with the diets and their perceptions of their cat's overall health.

Feeding Iams Hairball Care™ resulted in a reduction in the mean number of total hairballs reported per household per week of 22%, from 2.2 to 1.7 hairballs ( $P=.05$ ). Vomiting frequency was also reduced by 22%, from 3.8 to 3.0 occurrences per household per week on average when the Iams Hairball Care™ was fed ( $P<.05$ ). Participants in this study had a more positive impression of the diet and their cats' overall health with regards to the Iams Hairball Care™ diet.

Although hairballs are rarely a serious health threat, they are certainly not a pleasant experience for the cat. (If we vomited 4 times a month, wouldn't we want to eliminate or reduce that occurrence? Why consider something similar acceptable for our feline companions?) As a cat owner, finding a hairball in the dark with your foot is not a pleasant experience either. This experience and the associated mess probably accounts for hairballs consistently being ranked as one of the top negatives associated with cat ownership. This study is the first reported controlled evaluation of the effectiveness of a diet in managing hairballs in an in-home situation.

## DIETARY MANAGEMENT OF DIARRHEA

Dogs that are boarded in kennels or dogs taken into a shelter will commonly have diarrhea, which may be due in large part to the stress of the change in environment. The diarrhea in many of these cases is self limiting and will eventually resolve without specific treatment. Could dietary management help expedite this recovery process? That was the question examined in a study of dogs entering a no-kill shelter.

Dogs that had or developed diarrhea in the first 36 hours of entering a shelter were enrolled in the study. The cases studied had diarrhea defined as average stool rating less than 3 on a 5-point scale for at least 2 days (Table 2). Dogs studied were not treated with anti-parasitic, anti-inflammatory, antibiotics or anti-diarrheal agents. Eligible dogs were alternately assigned to one of two study diets, either Eukanuba Veterinary Diets® Nutritional Intestinal Formula™ Low Residue Adult/Canine (Low-Residue™) or Hill's® Prescription Diet® i/d® Canine (i/d®); both foods were dry formulas.

The dogs were fed the diets according to label guide-

lines to maintain body weight. Stool scores were recorded twice a day, once in the morning and once in the afternoon, with the average of the two scores representing the average daily stool score. Dogs were evaluated in this way for a minimum of 14 days. Twenty dogs were evaluated according to these guidelines.

The dogs managed with Low-Residue™ showed improvement more quickly (reduced time to the turning point) and resolved their diarrhea sooner than dogs managed with i/d® (Figure 1). The time to the turning point is the time to the first day that the stool score improved for at least two consecutive days. The time to resolution is the time it took to reach an average stool score of 3 or better. The time to the turning point for the Low-Residue™ diet was 3 days compared to 6 days for the i/d® diet. The time to resolution of diarrhea for Low-Residue™ was 8 days vs. 13 days for i/d®.

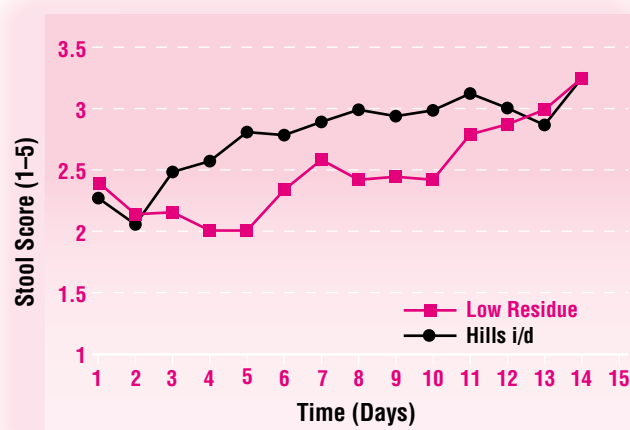


Figure 1. Average daily stool scores.

The faster response to management with Low-Residue™ is also reflected in the average weekly stool scores summarized in Table 3. The frequency of diarrhea at the twice daily evaluations was reduced by 30% in week one and by 45% in week two through management with Low-Residue™ compared to management with i/d®.

In this kennel situation more effective dietary management with Eukanuba Veterinary Diets® Low Residue™ is not only positive for the well-being of the dogs, but also has

Table 2.

### STOOL RATING SCALE

- 1 liquid with or without particulate matter
- 2 soft, shapeless
- 3 soft, but holds shape
- 4 firm, well formed stool, ideal score
- 5 Extremely hard, dry

Table 3.

### AVERAGE STOOL SCORES

Diet	Week 1	Week 2
Low Residue™	2.56 <sup>a</sup>	3.04 <sup>a</sup>
Hill's® i/d®	2.22 <sup>b</sup>	2.73 <sup>b</sup>

Different superscripts are different within week at  $P<0.05$

a positive impact on the management of the kennel. Reductions in the frequency of diarrhea and its duration help reduce the labor required to clean the kennels.

## THE BENEFIT OF WEIGHT LOSS IN DOGS WITH HIP OSTEOARTHRITIS

Obesity is recognized as an important factor influencing the clinical expression of osteoarthritis in humans.<sup>7-9</sup> While veterinarians have used nutritional therapy to achieve weight reduction in overweight osteoarthritic dogs, no data describing the effect of weight loss on lameness severity or the effect of weight loss on the prevalence or progression of osteoarthritis in dogs has been described. Because osteoarthritis of the hip joint is an important cause of lameness in dogs of all ages,<sup>4</sup> the following study was conducted using naturally-occurring cases of obese dogs with hip osteoarthritis to evaluate the hypothesis that lameness severity would be significantly influenced by weight loss.

The influence of weight reduction on pelvic limb function was prospectively examined in nine overweight client-owned dogs with hip osteoarthritis and lameness. Dogs studied were at least 10% over their ideal body weight. Numerical rating and visual analogue scales were used to subjectively assess lameness (by JI) prior to the dogs beginning a weight loss program. The weight loss program included feeding Eukanuba Veterinary Diets® Nutritional Weight Loss Formula™ Restricted-Calorie™/Canine at 60% of maintenance calories for initial body weight.

Lameness assessment was repeated at the mid-point and end of the 10 to 19 week weight loss period. The effect of time on lameness and body condition were evaluated using repeated-measures analysis-of-variance and the Friedman test. Differences were considered significant at  $P < .05$ . Over the weight loss period, dogs lost between 11 and 18% of their initial body weight. Body weight decreased linearly over time ( $P < .001$ ) and body condition score improved ( $P < .05$ ). Numerical rating scale (NRS) lameness scores improved significantly with time ( $P < .05$ ) and there was also a linear improvement in visual analogue scale (VAS) scores with time ( $P < .005$ ). Visual analog scale assessment scores for lameness improved 76% over the study period. No dog was withdrawn from the study because of worsening lameness.

Data from this study support the hypothesis that lameness severity can be significantly influenced by weight loss. Weight loss alone can result in a significant decrease in lameness. Increased emphasis should be placed on normalizing body weight in dogs with hip osteoarthritis. Although not examined in this study, normalization of the body weight of the osteoarthritic patient also has the potential to slow disease progression.

Current medical treatments for the management of dogs with osteoarthritis are primarily symptomatic. Longer treatment courses using nonsteroidal antiinflammatory drugs

should not be given without using a concurrent nutritional program to normalize the dog's body weight. Many overweight dogs with lameness due to hip osteoarthritis may not require drug treatment after excess weight has been lost.

## ACHIEVING WEIGHT LOSS

Weight loss in dogs can sometimes be difficult to achieve. As in this study it is advisable to thoroughly evaluate the patient before beginning an obesity management program. Start with a dietary history to determine the types and quantities of food fed, feeding patterns including times fed per day and who feeds the pet. Also evaluate the activity level and overall lifestyle of the pet. You may need to continue to probe to get a complete picture of the situation, such as does anyone else (a neighbor?) feed or treat the dog? Also important is a physical exam including a serum chemistry panel with thyroid screen and urine tests to rule out medical conditions such as diabetes, hyperthyroidism or hypothyroidism, hyperadrenocorticism, and heart disease.

Next evaluate the patient's weight. Comparing the dog's weight to breed standards where appropriate can be a first step to evaluating the degree of obesity. Given the wide ranges within breeds and the popularity of mixed-breed dogs, assigning a Body Condition Score (BCS) may be a more practical approach to determining level of obesity. Determining a BCS requires a visual **and tactile evaluation** of the ribs, spine, pelvis, waist, and abdomen (*see Figures 6 and 7 in S. Center chapter in this proceedings*). If you don't put your hands on the dog you have not completed an accurate BCS!

One of the most important factors in achieving successful weight loss (including the weight loss in this study) is to involve the owner. The owner must want the pet to lose weight. Recognition of the dog's obesity is a big step in enlisting the owner's commitment to weight loss. Demonstrate to the owner using visual cues or palpation that the dog is overweight. Ensure that the client understands the health risks associated with obesity.

For the purposes of this study specific weight loss goals, timelines and periodic weigh-ins were established and agreed to from the beginning. The same holds for any successful weight loss program. Setting short- and long-term weight loss goals with target dates for the owner allows for interim goals with positive reinforcement. These weigh-ins can be every 1–2 weeks at first to ensure the program gets off to a good start and can be less frequent as the program progresses.

Determine the daily caloric allotment that will achieve the targeted degree of weight loss and ultimate BCS. Be sure the client understands that this allotment may change during the program, depending on the amount of exercise and/or metabolic adaptations that occur. Make the client responsible for restricting the food appropriately. Encourage them to measure and record all food given. Involve everyone in the household who provides treats or food for the dog.

Although an exercise regime was not included as part

of this study, exercise can play an important role in weight loss. Varying degrees of exercise can be prescribed, depending on the health of the client and the patient. Goals can be set for increasing duration and intensity of exercise, but keep it reasonable. Exercise is just one additional facet of the entire weight loss program.

Provide support and positive reinforcement. Celebrate success. For the purposes of this study, client rewards (such as a leash) for reaching certain study weight loss milestones were provided. Rewards need not be expensive. Inexpensive but meaningful rewards such as a certificate documenting the target weight loss and progress toward that goal serves both as a reminder and a reward.

## DIETARY CONSIDERATIONS

The major contributing factor to obesity is excess caloric intake in relation to the dog's caloric requirements.<sup>10</sup> In this study Eukanuba Veterinary Diets<sup>®</sup> Nutritional Weight Loss Formula<sup>™</sup> Restricted-Calorie<sup>™</sup>/Canine (Restricted-Calorie<sup>™</sup>) was fed at 60% of maintenance calories for initial body weight. Several features of this diet help to acceptably reduce caloric intake.

By replacing some dietary fat with carbohydrate instead of fiber, the caloric density of the Restricted-Calorie<sup>™</sup> diet is reduced while maintaining a high level of nutrition. Carbohydrate contains less than half the calories of fat, which allows clients to feed an amount of food they perceive as adequate while reducing calories consumed by the pet. Reduced quantities of fat necessitate attention to the type and quality of the dietary fat. Ensuring that the ratio of omega-6:omega-3 fatty acids is between 5:1 and 10:1 will help promote healthy skin and coat during weight loss.

Likewise, it is important to carefully select the starch sources used to replace fat in the diet. The carbohydrate component of pet foods provides the primary source of the increase in blood glucose after a meal. Starch sources behave very differently in the way that they influence blood glucose and insulin responses. Grain sorghum and barley are utilized as starch sources in the Restricted-Calorie<sup>™</sup> diet. This results in lower postprandial blood glucose levels and lower blood insulin levels than if other starch sources such as wheat or rice are used as the source of starch.<sup>11</sup> By minimizing postprandial increases in blood glucose and insulin, specially formulated foods containing a blend of barley and grain sorghum may help improve glucose intolerance and stabilize blood glucose levels in overweight pets.

Caloric density of the diet may also be reduced by the addition of fiber to the diet. The Restricted-Calorie diet contains normal levels of moderately fermentable fiber instead of high levels of non-fermentable fiber such as cellulose. Increased non-fermentable fiber levels can result in increased stool volume, poor skin and coat quality, and ultimately result in poor client compliance.

## ENHANCING WEIGHT LOSS

Other dietary approaches, beyond feeding a low-fat, low-calorie diet to assist with canine weight management is to affect the way nutrients are metabolized to help promote weight loss and improve body composition. Chromium can help optimize body composition during weight loss. Dogs fed diets containing supplemental chromium (as chromium tripicolinate) had greater loss of fat mass compared with that from feeding a carnitine-supplemented diet.<sup>12</sup> In addition to its role in improving body composition during weight loss, dogs fed diets supplemented with chromium tripicolinate had improved glucose tolerance and an increased rate of glucose removal from the bloodstream after intravenous glucose infusion.<sup>13</sup> By enhancing tissue use of glucose, diets containing chromium tripicolinate may lead to an overall improvement in glucose tolerance and blood glucose stability in overweight pets.

Another dietary component that can affect nutrient metabolism is carnitine. Carnitine is a water-soluble, vitamin-like compound made in the body from the amino acids lysine and methionine. It is naturally present in animal-based protein ingredients. By forming acyl-carnitines, carnitine “escorts” fatty acids into the cells' mitochondria for oxidation and energy production. In this way, carnitine helps reduce body fat storage and blood lipid levels. When added to a canine weight-loss diet, carnitine resulted in a tendency for lower fat mass and greater lean body mass, even with greater energy intake.<sup>14</sup>

Achieving weight loss in overweight dogs can be challenging. However, successful weight loss can be achieved by engaging the owner, agreeing to achievable weight loss milestones with positive feedback and by using diets with dietary features that can help achieve the desired weight loss. Additional motivation for successful weight loss can also be derived from the observable improvement in lameness as lame overweight dogs lose weight.

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# Common Complications of Insulin Therapy in Diabetic Cats

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## INTRODUCTION

Establishing an effective treatment regimen for diabetes mellitus is often challenging in cats. Variables such as severity of pancreatic beta cell loss, responsiveness of tissues to insulin, presence or absence of glucose toxicity, problems with absorption and duration of effect of exogenously-administered insulin, asymptomatic hypoglycemia and induction of glucose counterregulation, and presence and reversibility of concurrent disease affect the success of treatment, lead to confusion and frustration for the veterinarian and owner, and create the perception that feline diabetes mellitus is a difficult disease to treat. The purpose of this article is to briefly discuss several of the commonly encountered problems that impact the success of treatment—problems which should be considered whenever control of glycemia becomes difficult in the diabetic cat.

## FLUCTUATING INSULIN DEPENDENCY

Insulin dependency is unpredictable in diabetic cats. Some diabetic cats always require insulin, some cats rarely

require insulin, and some cats oscillate between needing and not needing insulin to control the diabetic state. The severity of destruction of pancreatic beta cells and the presence, severity, and reversibility of concurrent disorders that negatively affect insulin sensitivity are perhaps the two most important factors dictating insulin dependency in diabetic cats. Destruction of pancreatic beta cells can be rapid and complete and insulin-dependent diabetes mellitus (IDDM) may exist at the time diabetes is diagnosed. Alternatively, cats may gradually lose the ability to secrete insulin if beta cells are destroyed slowly. These cats may have an initial period when hyperglycemia and clinical signs of diabetes can be controlled with treatments other than insulin (ie, non-insulin-dependent diabetes mellitus [NIDDM]). However, if the underlying pathologic process causing destruction of beta cells is progressive, eventually the ability to secrete insulin is lost and IDDM develops. The progression from NIDDM to IDDM is unpredictable and dependent, in part, on the type and progression of islet pathology and the reversibility of concurrent insulin resistant disease.

The presence and severity of insulin resistance is an important variable that influences the clinical picture in cats with partial destruction of pancreatic beta cells. Insulin resistance increases the demand for insulin secretion by beta cells; a demand which may not be met in some cats with partial loss of beta cells. The more severe the insulin resistance and the more severe the loss of beta cells, the more likely hyperglycemia will develop. Persistent hyperglycemia can, in turn, suppress function of remaining beta cells, causing hypoinsulinemia and worsening hyperglycemia; a syndrome referred to as glucose toxicity.<sup>1</sup> Examples of concurrent insulin-resistant disorders include obesity, chronic pancreatitis and other chronic inflammatory diseases, infection, and insulin-resistant disease like hyperthyroidism, hyperadrenocorticism and acromegaly (**Table**). Identification and correction of concurrent problems that

**Table.** *Recognized causes of insulin resistance in diabetic cats*

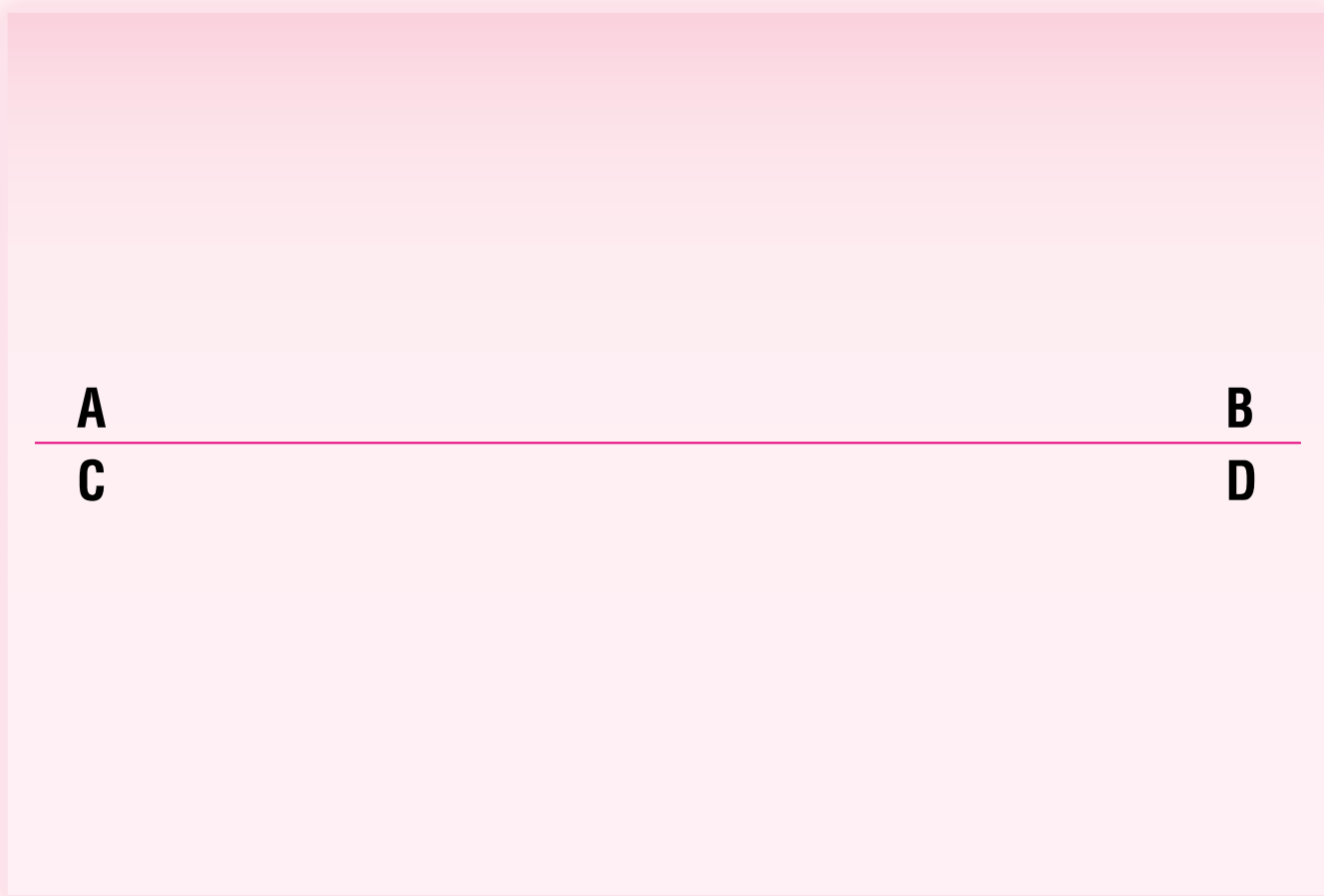
<b>Disorders Typically Causing Severe Insulin Resistance</b>	<b>Disorders Typically Causing Mild or Fluctuating Insulin Resistance</b>
Hyperadrenocorticism	Obesity
Acromegaly	Chronic Pancreatitis
Progesterone excess	Disease of the oral cavity
Diabetogenic drugs (most notably glucocorticoids)	Chronic inflammation
	Renal insufficiency
	Liver insufficiency
	Hyperthyroidism
	Infections
	Pancreatic exocrine insufficiency
	Hyperlipidemia
	Neoplasia

affect insulin sensitivity is critical to the successful treatment of diabetes in cats, regardless of the health of the beta cells.

In cats with partial loss of beta cells, improvement in insulin sensitivity may cause reversion from an insulin-dependent to a noninsulin dependent or subclinical diabetic state.<sup>1</sup> Obesity-induced carbohydrate intolerance is the classic insulin-resistant disorder affiliated with development of NIDDM in humans and has been identified as a potential causative factor in the development of diabetes in cats as well.<sup>2,3</sup> Obesity causes a reversible insulin resistance that is a result of down-regulation of insulin receptors, impaired receptor binding affinity for insulin, and postreceptor defects in insulin action.<sup>4</sup> The abnormalities responsible for insulin resistance are reversible with correction of obesity, which is why correction and prevention of obesity is always an important component of the treatment regimen for dia-

betes.<sup>5-6</sup> With weight loss, insulin resistance improves, exogenous insulin becomes more effective in controlling glycemia, and insulin administration can be discontinued in some diabetic cats.

A sustained demand for insulin secretion in response to insulin resistance can also lead to worsening islet pathology, a further reduction in the population of beta cells, and ultimately IDDM. Islet amyloidosis is a classic example of this concept. Amyloid is a common pathologic finding in the pancreatic islets of diabetic cats (**Figure 1**). Amylin is the principle constituent of islet amyloid, is located within beta cell secretory granules, and is co-secreted with insulin by the beta cell.<sup>7,8</sup> Stimulants of insulin secretion also stimulate the secretion of amylin. Amylin acts as a neuroendocrine hormone with several glucoregulatory effects that collectively complement the actions of insulin in postprandial



**Figure 1.** Pancreatic islets from one healthy cat and three cats with diabetes mellitus. Pancreatic islets have been stained for insulin and illustrate differences in loss of beta cells between diabetic cats. Insulin-containing beta cells stain orange in color. (Note that in the photos shown here, the insulin-containing beta cells appear dark pink.)

- A.** Normal population of beta cells in a healthy cat.
- B.** Mild loss of beta cells and minimal pathologic changes in the islet in a cat with noninsulin-dependent diabetes mellitus treated with diet and glipizide
- C.** Islet amyloidosis and moderate to severe loss of beta cells in a cat with initial noninsulin-dependent diabetes mellitus that progressed to insulin-dependent diabetes mellitus. Pancreatic biopsy was obtained during insulin-dependent diabetic state.
- D.** Severe islet amyloidosis and absence of beta cells in a diabetic cat with insulin-dependency beginning at the time diabetes was diagnosed. (Immunoperoxidase stain, x100)



glucose control.<sup>9,10</sup> Chronic increased secretion of insulin and amylin, as occurs with obesity and other insulin resistant states, results in aggregation and deposition of amylin in the islets as amyloid (**Figure 2**). Amylin-derived amyloid fibrils are cytotoxic and associated with apoptotic cell death of islet cells.<sup>11,12</sup> If deposition of amyloid is progressive, as occurs with persistent insulin resistant states such as obesity, islet cell destruction progresses and the cat will progress from a subclinical diabetic state to NIDDM and ultimately to IDDM.

Our current understanding of the etiopathogenesis of diabetes in the cat suggests that the difference between IDDM and NIDDM is primarily a difference in severity of loss of beta cells and severity and reversibility of concurrent insulin resistance. Most cats with IDDM and NIDDM have islet amyloidosis, vacuolar degeneration of beta cells, or islet hypoplasia.<sup>1,13</sup> The more severe the islet pathology, the more likely the cat will have IDDM, regardless of concurrent insulin resistance (**Figure 1**). The less severe the islet pathology, the greater the role of concurrent insulin resistance in dictating whether the cat has IDDM or NIDDM. The more severe and the less reversible the cause of the insulin resistance, the more likely the cat with mild islet pathology will be insulin-dependent, and vice versa. Fluctuations in severity of insulin resistance, as occurs with chronic pancreatitis, can cause a cat with mild islet pathology to oscillate between IDDM and NIDDM as the severity of pancreatic inflammation and insulin resistance waxes and

wanes. Persistent insulin resistance may cause progressive loss of beta cells, worsening insulin deficiency, and eventually IDDM.<sup>1,14</sup>

## VARIABLE EFFECTIVENESS OF INSULIN PREPARATIONS

Diabetic cats are notoriously unpredictable in their response to exogenous insulin. There is no single type of insulin which is routinely effective in maintaining control of glycemia, even with twice-a-day administration. Ultralente insulin is the longest-acting but least potent of the commonly-used commercial insulins. Although considered a long-acting insulin, ultralente insulin has to be administered twice a day in most diabetic cats and absorption of ultralente insulin is inadequate for controlling glycemia in approximately 25% of cats. Lente and NPH insulin are more potent insulin preparations that are more consistently and rapidly absorbed following subcutaneous administration than ultralente insulin. Unfortunately, the duration of effect of lente and especially NPH insulin can be considerably shorter than 12 hours in some diabetic cats, resulting in inadequate control of glycemia despite twice-a-day administration.

Protamine-zinc insulin (PZI) is a longer acting insulin that is more consistently absorbed than ultralente insulin and has a more acceptable duration of effect than NPH insulin. However, the timing of the glucose nadir is quite variable and occurs within 9 hours of PZI administration in greater than 80% of treated diabetic cats.<sup>15</sup> We routinely administer PZI insulin twice a day. In a recent study, PZI was very effective in significantly improving control of glycemia in newly diagnosed diabetic cats and poorly-controlled diabetic cats previously treated with ultralente or NPH insulin.<sup>15</sup> Comparison of efficacy between PZI and lente insulin has not been reported.

Insulin glargine is a long-acting insulin analog that forms microprecipitates at the site of injection from which small amounts of insulin glargine are slowly released. In humans, the slow sustained release of insulin glargine from these microprecipitates results in a relatively constant concentration/time profile over a 24 hour period with no pronounced peak in serum insulin. Insulin glargine is currently recommended as a basal insulin (ie, sustained long-acting insulin to inhibit hepatic glucose production) administered once a day at bedtime in human diabetics.<sup>16-17</sup>

In a preliminary study involving healthy cats, most of the pharmacokinetic pharmacodynamic properties (ie, onset of action, glucose nadir, time for blood glucose concentration to return to baseline, mean daily blood glucose concentration, and area under the 24-hour blood glucose curve) were similar for insulin glargine and PZI. Similar studies in diabetic cats have yet to be reported. In our experience, insulin glargine has a duration of effect ranging from 10 to 16 hours in most diabetic cats. We have not yet encountered prob-



**Figure 2.** Schematic of the interplay between insulin resistance, amylin secretion, and amyloid deposition in the pancreatic islets. Insulin secretion increases to compensate for insulin resistance induced by environmental factors, insulin-antagonistic drugs, and concurrent illness. Because amylin and insulin are co-secreted, amylin secretion also increases in insulin-resistant states. If sustained, increased amylin secretion can lead to amylin aggregation and the formation of amyloid in the islets. (From Feldman EC, Nelson RW. *Canine and Feline Endocrinology and Reproduction*, 3rd ed. Philadelphia, WB Saunders Co, 2004; in press.)

lems with inadequate absorption of insulin glargine, as described with ultralente insulin, although it seems likely that this problem will be encountered as we gain more experience with this insulin analog. Currently, we consider using insulin glargine in diabetic cats with problems of short duration of effect of NPH, lente, and PZI insulin.

It is not possible to predict which type of insulin will work best in individual diabetic cats. The initial insulin of choice ultimately is based on personal preference and experiences. Currently, we recommend either lente or PZI insulin at a dosage of 1 to 2 U per cat administered twice daily. Dietary therapy is initiated concurrently. Because greater than 80 to 90% of diabetic cats require insulin twice a day, we prefer to start with twice-a-day insulin therapy. Establishing control of glycemia is easier and problems with hypoglycemia and glucose counterregulation are less likely when twice daily insulin therapy is initiated while the insulin dose is low; ie, at the time insulin treatment is initiated.

## ASYMPTOMATIC HYPOGLYCEMIA AND GLUCOSE COUNTERREGULATION

Asymptomatic hypoglycemia is a common complication of insulin therapy in diabetic cats. In a recent study evaluating the efficacy of PZI insulin in 67 diabetic cats, asymptomatic hypoglycemia (defined as a blood glucose concentration less than 80 mg/dl) was identified in 24 (9%) of 268 9-hour blood glucose curves and in 21 (31%) of 67 cats.<sup>15</sup> The median daily insulin dosage at the time asymptomatic hypoglycemia developed was 0.8 U/kg, with a range of 0.4 to 1.4 U/kg. When hypoglycemia develops or when the blood glucose concentration decreases rapidly regardless of the glucose nadir, direct hypoglycemia-induced stimulation of hepatic glycogenolysis and secretion of diabetogenic hormones, most notably epinephrine and glucagon, increase the blood glucose concentration, minimize signs of hypoglycemia, and cause marked hyperglycemia within 12 hours of glucose counterregulation. The marked hyperglycemia that occurs after hypoglycemia is due, in part, to an inability of the diabetic cat to secrete sufficient endogenous insulin to dampen the rising blood glucose concentration. Secretion of diabetogenic hormones during the hypoglycemic episode may induce insulin resistance, which can last 24 to 72 hours after the hypoglycemic episode.

Clinical signs of hypoglycemia are typically mild or not recognized by the owner; clinical signs caused by hyperglycemia tend to dominate the clinical picture. The insulin dose that induces hypoglycemia is variable and unpredictable, can be induced with insulin dosages less than 0.4 U/kg per injection, and can result in cats receiving 10 to 15 units of insulin per injection as veterinarians react to the persistence of clinical signs and high blood glucose and serum fructosamine concentrations by increasing the insulin dose and perpetuating the problem. If a serial blood glucose curve is obtained on the day glucose counterregulation occurs, hypoglycemia will be identified and the diag-

nosis established. However, if the serial blood glucose curve is obtained on a day when insulin resistance predominates, hypoglycemia will not be identified and the insulin dose may be incorrectly increased in response to the high blood glucose values. A cyclic history of one or two days of good glycemic control (ie, minimal clinical signs) followed by several days of poor control should raise suspicion for insulin resistance caused by glucose counterregulation. Serum fructosamine concentrations are unpredictable but are usually increased (>500  $\mu\text{mol/l}$ ); such results confirm poor glycemic control but do not identify the underlying cause.

Insulin-induced hypoglycemia and rebound hyperglycemia induced by glucose counterregulation was originally described in diabetic humans by Dr. Somogyi in the 1930's and subsequently became known as the Somogyi phenomenon.<sup>19</sup> Asymptomatic hypoglycemia and its physiologic consequences is one of the most common causes of poor control of glycemia in insulin-treated diabetic cats and should always be considered, regardless of the insulin dose being administered. Treatment involves arbitrarily reducing the insulin dose 1 to 2 units per injection and evaluating the cat's clinical response over the ensuing 2 to 5 days, or starting glycemic regulation over using an insulin dose of 1 unit per injection twice a day.

## FLUCTUATING INSULIN REQUIREMENTS

One of the most frustrating problems encountered with insulin treatment is the sudden inability to maintain control of glycemia in a previously well-controlled diabetic cat. Typically, the diabetic cat has been well-controlled with a consistent dose of insulin for weeks to months and then suddenly becomes symptomatic (eg, lethargy, weakness, polyuria polydipsia, weight loss). Concurrent problems are not readily apparent and an increase in the insulin dose may improve clinical signs for a short period of time (days to weeks), only to have clinical signs recur and often improve with a further increase in the insulin dose. If this routine continues, the insulin dose may eventually exceed 1.5 to 2.0 U/kg/injection with variable but inconsistent improvement in clinical signs.

Control of glycemia often remains erratic and unpredictable and the insulin dose is changed frequently in an attempt to reestablish consistent control of glycemia. Hypoglycemia may suddenly be identified despite weeks to months of poor control and consistently high blood glucose concentrations. In many cats, the increased frequency of visits to the veterinary hospital and blood glucose measurements ultimately leads to stress-induced hyperglycemia and the frustration of the veterinarian and owner intensifies.

In our experience, the most common explanation for sudden loss of glycemic control in a previously stable diabetic cat is development of a concurrent disorder causing insulin resistance. The insulin resistance is usually mild and either spontaneously reversible or oscillates in severity over time (**Table**). Inflammatory disorders such as mild chronic

pancreatitis that typically go unrecognized by the owner and veterinarian are the most common culprits. In a diabetic cat receiving a fixed dose of insulin, the development of insulin resistance results in hyperglycemia and recurrence of clinical signs. An increase in the insulin dose will improve control of glycemia because the insulin resistance is relatively mild. If the insulin resistance worsens, further increases in the insulin dose will be required to maintain control of glycemia. However, if and when insulin resistance improves or resolves, the cat is suddenly at risk for developing hypoglycemia, glucose counterregulation, and persistent poor control of the diabetic state. In essence, what started out as an insulin resistance problem causing loss of glycemic control evolves into poor glycemic control because of the Somogyi phenomenon; the latter developing from an insulin overdose created when the inflammatory process subsides and insulin resistance improves (**Figure 3**). A thorough history, physical examination, evaluation of a serial blood glucose curve, and if indicated, diagnostic evaluation for disorders known to cause insulin resistance in the diabetic cat should be undertaken whenever a previously well-controlled diabetic cat suddenly becomes symptomatic for the disease. Hypoglycemia inducing glucose counterregulation should always be considered if a reason for the sudden deterioration in glycemic control is not evident after a thorough evaluation of the cat, especially if the insulin dose has been arbitrarily increased prior to the evaluation.

### OCCULT STRESS-INDUCED HYPERGLYCEMIA

Hyperglycemia induced by stress, aggression or excitement is the single biggest problem affecting accuracy of blood glucose measurements in cats. Stress can override the glucose-lowering effect of the insulin injection, cause high blood glucose concentrations, and if unrecognized lead to a spiraling path of insulin overdose, hypoglycemia, glucose counterregulation, and poor control of glycemia. The biggest factors inducing stress hyperglycemia are hospitalization and multiple venipunctures. Most diabetic cats do not tolerate frequent venipunctures and eventually develop a change in temperament, typically towards aggression, and stress hyperglycemia. Induction of stress hyperglycemia is variable but usually starts during a venipuncture procedure and begins earlier and earlier on subsequent visits to the veterinarian, until eventually stress hyperglycemia is induced by hospitalization and ultimately by the car ride to the veterinary hospital.

Blood glucose concentrations can remain greater than 400 mg/dl throughout the day when stress hyperglycemia develops prior to the first venipuncture of the day, despite administration of insulin (**Figure 4**). Failure to recognize the effect of stress on blood glucose results may lead to the erroneous perception that the diabetic cat is poorly-controlled. Insulin therapy is invariably adjusted, often by increasing the insulin dosage, and another blood glucose curve recommended 1 to 2 weeks later. A vicious cycle

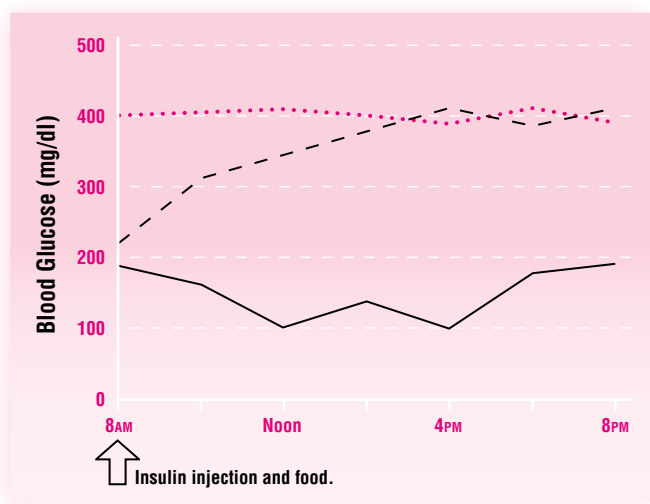
ensues, which eventually culminates in hypoglycemia, glucose counterregulation, and referral for evaluation of insulin resistance. Failure to identify the presence of stress hyperglycemia and its impact on interpretation of blood glucose measurements is one of the most important reasons for misinterpreting the status of glycemic control in diabetic cats.

Veterinarians must remain wary of stress hyperglycemia in diabetic cats and should take steps to avoid its development. Micro-managing diabetic cats should be avoided and serial blood glucose curves should only be done when there is a perceived need to change insulin therapy. The determination of good versus poor control of glycemia should be based on the owner's subjective opinion of presence and severity of clinical signs and overall health of their pet, ability of the cat to jump, its level of activity and grooming behavior, findings on physical examination, and stability of body weight. Serial blood glucose measurements are indicated if poor control of glycemia is suspected. The purpose of serial blood glucose measurements is to obtain a glimpse at the actions of insulin in that diabetic cat and hopefully identify a reason (eg, short duration of insulin effect) that could explain why the diabetic cat is poorly controlled.



**Figure 3.** Schematic of the interplay between insulin resistance, hypoglycemia and glucose counterregulation, and stability of glycemic control. Development of insulin resistance has a deleterious impact on control of glycemia, which is often corrected by increasing the dosage of insulin. Worsening insulin resistance leads to additional increases in the insulin dosage to maintain control of glycemia. Spontaneous improvement in insulin resistance without a corresponding decrease in the insulin dosage may result in asymptomatic hypoglycemia, glucose counterregulation, and a transition from erratic glycemic control caused by insulin resistance to erratic glycemic control caused by the Somogyi phenomenon.

Stress hyperglycemia should be suspected if the cat is visibly upset, aggressive or struggles during restraint and the venipuncture process. But stress hyperglycemia can also be present in diabetic cats that are easily removed from the cage and do not resist the blood sampling procedure. These cats are scared but rather than become aggressive, they remain crouched in the back of the cage, often have dilated pupils, and do not resist handling. Stress hyperglycemia should also be suspected when there is disparity between assessment of glycemic control based on results of the history, physical examination and stability of body weight, and assessment of glycemic control based on results of blood glucose measurements, or when the initial blood glucose concentration measured in the morning is in an acceptable range (ie, 150 to 250 mg/dl) but subsequent blood glucose concentrations increase steadily throughout the day (**Figure 4**). Once stress hyperglycemia develops it is a perpetual problem and blood glucose measurements can no longer be considered accurate. If stress hyperglycemia is suspected, a switch from reliance on serial blood glucose curves generated in the veterinary hospital to reliance on blood glucose results generated by the owner in the less stressful home environment (ie, marginal ear vein prick technique)<sup>20</sup> or evaluation of serum fructosamine concentrations obtained prior to and 2–3 weeks after adjusting the insulin treatment regimen should be done, in addition to the history and physical examination findings.



**Figure 4.** Blood glucose curves in a 5.3 kg male cat receiving 2 U recombinant human Ultralente insulin (solid black line) 2 weeks after initiating insulin therapy, 2 U recombinant human Ultralente insulin (dashed black line) 2 months later, and 6 U recombinant human Ultralente insulin (dotted pink line) 4 months later. The insulin dosage had been gradually increased based on results of blood glucose curves. The owner reported minimal clinical signs regardless of the insulin dosage and the cat had maintained its body weight. The cat became progressively more fractious during each hospitalization, supporting stress-induced hyperglycemia as the reason for the discrepancy between blood glucose values and other parameters used to evaluate glycemic control. (From Feldman EC, Nelson RW. *Canine and Feline Endocrinology and Reproduction*, 2nd ed. Philadelphia, WB Saunders Co, 1996; 373.)

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# Nutritional Management of Glycemia and Diabetes

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## INTRODUCTION

Impairments in normal glucose metabolism in dogs and cats occur in association with a number of conditions and life stages. These include overweight and obese conditions, aging, gestation, and diabetes mellitus (DM). In many animals, poor glycemic control initially manifests as insulin resistance, which leads to compensatory hyperinsulinemia as the body attempts to maintain normoglycemia. Diabetes mellitus occurs when pancreatic beta cells can no longer produce adequate insulin in the face of insulin resistance (ie, beta cell “exhaustion”), or as a result of beta cell destruction or loss from other causes.<sup>1,2</sup> In humans these are referred to as type II and type I DM, respectively. However, these classifications may not always accurately describe progression of DM in dogs and cats.<sup>3,4</sup> The metabolic abnormalities that accompany DM include increased fasting blood glucose and

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insulin, and prolonged postprandial blood glucose and insulin levels (ie, decompensated insulin resistance). Dietary control of hyperglycemia and hyperinsulinemia are important for the management of impaired glycemic response and may play an important role in slowing or preventing the onset of beta cell dysfunction in insulin resistant animals.

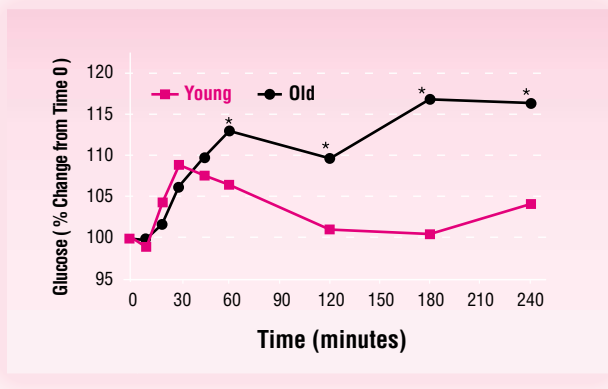
## INCIDENCE AND RISK FACTORS

Recent studies of case records in the Veterinary Medical Database (VMDB) have reported significant increases in the incidence rate of DM for both dogs and cats.<sup>5,6</sup> Animals diagnosed with DM between 1970 and 1999 were studied to determine hospital prevalence and fatality rates over a 30-year period. The incidence rate in cats has increased dramatically, from 8 cases per 10,000 admissions in 1970 to 123 cases per 10,000 admissions in 1999. A significant increase also occurred in dogs, from 19 cases to 64 cases per 10,000 annual admissions. In contrast, case fatality rates decreased significantly over the same time period, from 40 to 10% for cats and from 37 to 5% in dogs. The decreased fatality rates suggest that owners and veterinarians may be more willing to commit to the long-term management and treatment of pets with DM. The trend may also reflect advancements in the treatment and nutritional management of pets with poor glycemic control.

In humans, the incidence of type 2 DM has closely paralleled the rising incidence of obesity in the United States.<sup>7,8</sup> The association between overweight body condition and changes in glucose metabolism, with or without the development of DM, is well documented in humans.<sup>7,9</sup> Similarly, obesity is the most common nutritional problem in pets today, with reported incidence rates between 25 and 44% of dogs and 20 and 35% of cats.<sup>10-13</sup> Similar to overweight humans, overweight dogs are more likely to be glucose intolerant and to experience hyperinsulinemia.<sup>14</sup> Cats that weigh 20% or more above their ideal BW have increased baseline glucose and peak glucose and insulin levels in response to intravenous glucose tolerance tests.<sup>15</sup> Cats that are overweight are at increased risk of developing insulin resistance compared with lean cats.<sup>16</sup> A recent study showed that insulin sensitivity was reduced by as much as 50% in cats that gained a large proportion of their body weight.<sup>17</sup>

An important risk factor for the development of impaired glycemic control in both dogs and cats is increasing age. More than 65% of diabetic cats are 10 years or older and a diagnosis of DM is very rare in kittens and young adult cats.<sup>4,18</sup> Changes in glycemic control occur without the development of DM as well. Older cats have been shown to have a diminished rate of glucose clearance following a glucose tolerance test, compared with young cats.<sup>19</sup> Similarly, older dogs are also at increased risk of developing impaired glucose tolerance and DM.<sup>5</sup> A study of glucose metabolism in old dogs (9.6 ± 0.2 years) compared with young dogs (0.7 ± 0.2 years) reported that young dogs had higher rates of postprandial glucose response while the

older dogs had delayed glucose responses and appeared to have increased insulin secretion (Figure 1).<sup>20</sup> These results are in agreement with studies in human subjects that have demonstrated increased insulin resistance with age.<sup>21</sup> Interestingly, there is evidence from studies with laboratory rats indicating that some of the age-associated changes in glycemic response can be influenced by diet.<sup>22</sup>



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

In cats, males are at increased risk of developing DM compared with females, and risk increases significantly in male cats who weigh more than 2.27 kg.<sup>6</sup> In contrast, female dogs are at greater risk for developing DM than are male dogs.<sup>5</sup> Other predisposing factors to glucose intolerance and DM in cats include inactivity, presence of pancreatic neoplasia, the long-term administration of progesterone or progestin, and possibly genetics.<sup>23-25</sup> A recent study showed that cats who were at ideal body weight but had relatively reduced insulin sensitivity were at the greatest risk of developing glucose intolerance when they gained weight.<sup>17</sup> Additional risk factors for dogs include recurrent episodes of pancreatitis, autoimmune-mediated pancreatic islet cell destruction, and a genetic (breed) predisposition.<sup>26-29</sup> Although purebreds as a whole are not at increased risk compared with mixed-breed dogs, certain breeds have a markedly increased chance of developing DM. These include the Australian Terrier, Standard Schnauzer, Miniature Schnauzer, and Samoyed.<sup>5</sup> Although less common, insulin resistance as a result of hypothyroidism, hyperadrenocorticism or the chronic administration of exogenous corticosteroids can also occur.<sup>30,31</sup>

## PRINCIPLES OF GLYCEMIC CONTROL

The ingestion of food results in a postprandial increase in blood glucose, which is followed by an increase in blood insulin levels. Dogs and cats with impaired glucose control do not efficiently store glucose and experience postprandial hyperglycemia for a longer period than normal animals. The glycemic response of dogs and cats with poor glucose

control can be improved by providing a diet that aids in normalizing blood glucose levels, enhances insulin sensitivity, and controls weight. A primary goal of nutritional management is to dampen the postprandial glucose response, thus minimizing large fluctuations in blood glucose levels. A diet that minimizes the glycemic response is desirable because lessening fluctuations in blood glucose contributes to better control of hyperglycemia and its associated health complications.

Traditional approaches to controlling blood glucose and managing DM in dogs and cats have focused on feeding diets that are high in various types of fiber. Some benefits are associated with this approach, but the singular use of high-fiber diets to the exclusion of other nutrients can negatively impact diet palatability and acceptability, nutrient digestibility, stool quality, and skin and hair coat quality.<sup>32</sup> An alternative nutritional approach improves glucose control through the provision of an appropriate caloric distribution of fat, protein and carbohydrate, and the inclusion of specific nutrients that enhance glycemic control. These nutrients include certain types of fiber and starches, chromium tripicolinate, and possibly vitamin A. Finally, the type of feeding regimen that is used (meal feeding vs. ad libitum) may help to modulate fluctuations in postprandial glucose and insulin.

## Caloric Distribution of Carbohydrate, Protein, and Fat

Feeding digestible carbohydrate can result in rapid increases in blood glucose and increases the demand for insulin secretion. Starch is the primary form of digestible carbohydrate in dog and cat diets, and is considered to be the major dietary component responsible for postprandial elevations in blood glucose.<sup>33</sup> It has been postulated that the long-term consumption of highly digestible carbohydrate may contribute to the eventual loss of beta cells because of chronically elevated demands for insulin.<sup>34</sup>

To examine the relationship between digestible carbohydrate and glycemic response, the effect of feeding high-protein, high-carbohydrate, or high-fat diets to adult cats was studied.<sup>35</sup> A group of 24 adult, neutered, normal weight cats was divided into 3 groups based upon sex, body weight, and plasma concentrations of glucose and insulin. Groups were randomly assigned to one of three test diets (Table). Cats were fed their assigned diet for 4 weeks and glucose tolerance tests in response to feeding were administered at the start and end of the feeding period. Cats fed the high-carbohydrate diet had significantly higher mean total and peak glucose values and mean Area Under Curve (AUC)<sub>glucose</sub> in response to the glucose tolerance test, compared with cats fed the high-protein and high-fat diets. Of the three diets, the high-protein diet resulted in the lowest values for mean glucose and AUC<sub>glucose</sub>, but the difference between the high-protein and the high-fat diet was not statistically significant. However, cats fed the high-fat diet had higher insulin:glucose ratios, which is suggestive of reduced insulin sensitivity.

**Table.** Caloric Distribution of Test Diets Fed to Normal Weight Cats<sup>a</sup>

Diet	Protein <sup>b</sup>	Carbohydrate <sup>b</sup>	Fat <sup>b</sup>
Pre-Test (Standard) Diet	28	26	48
High Protein	46	27	26
High Carbohydrate	25	47	26
High Fat	26	26	47

<sup>a</sup> Adapted from Reference #35  
<sup>b</sup> Expressed as % ME calories

Similar results have been reported in dogs. Feeding dogs high-fat diets promotes weight gain and is associated with the development of insulin resistance and obesity-associated hypertension.<sup>36-38</sup> An underlying mechanism for this effect may be related to levels of non-esterified fatty acids (NEFA) and betahydroxybutyrate (BHOB), compounds that both negatively affect insulin action. The study described previously also compared plasma NEFA and BHOB concentrations before and after the cats consumed diets high in either protein, fat or carbohydrate (**Table**).<sup>39</sup> Mean NEFA and BHOB serum concentrations in response to a meal were significantly reduced in cats fed the high-protein diet compared with initial values when fed the standard (high-fat) diet. Although only significant for BHOB, concentrations of both NEFA and BHOB also tended to decrease in cats fed the high-carbohydrate diet compared with initial values when fed the standard high-fat diet. Blood values for both NEFA and BHOB were highest when cats consumed diets containing 46% of calories from fat. When the data of all tests were combined, there was a significant negative correlation between NEFA concentration and insulin concentration ( $r = 0.97$ ;  $P = 0.007$ ). These results suggest that feeding reduced fat diets (26 % of calories) to cats will decrease blood NEFA and BHOB concentrations and may improve insulin sensitivity in pets with insulin resistance.

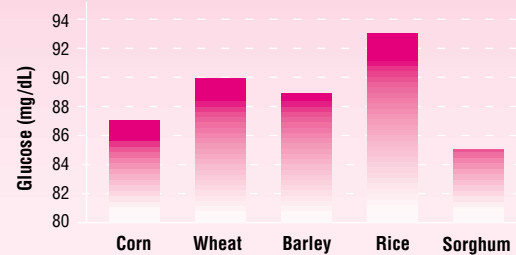
### Type of Starch

In addition to the amount of digestible carbohydrate that is included in diets for glycemic control, the source of the starch is also important. The term “glycemic index” refers to a ranking system that categorizes human foods based upon their effects on blood glucose levels.<sup>40</sup> It is commonly believed that all complex carbohydrates have a lower glycemic index than simple carbohydrates because the complex forms are more slowly digested. However, recent evidence shows that starch sources vary considerably in their glycemic effects, and some starch sources actually result in glycemic and insulinemic responses that are comparable to those of simple sugars.<sup>41,42</sup> A starch’s glycemic effect can be influenced by its relative proportions of amylose and amylopectin, its physical form and associated levels of fiber, and the type of food processing that is used.<sup>43-45</sup> For

example, in humans, blood glucose and insulin responses are higher when refined forms of wheat starch are consumed compared with responses to potato or barley starches.<sup>46-48</sup>

Because little information existed in dogs and cats, the glycemic responses of these species to various starches when included in food was studied. To examine this, a set of two crossover, replicate studies using adult, healthy dogs and cats were conducted.<sup>49,50</sup> Thirty weight-stable dogs and cats were randomly assigned to one of five dietary treatments and were fed their assigned diets for two weeks. Glycemic response tests were performed at the conclusion of each replicate period. The test diets were formulated to contain similar levels of starch from either corn, wheat, barley, rice or sorghum. Results demonstrated that dogs fed rice had the highest average postprandial glucose response and the greatest AUC<sub>glucose</sub> compared with dogs fed other sources of starch (**Figure 2**). Comparatively, dogs fed sorghum had the lowest average postprandial glucose response and lowest AUC<sub>glucose</sub>. Glucose responses to corn, wheat and barley were intermediate to those of sorghum and rice. Dogs fed rice had significantly higher average postprandial plasma insulin levels and greater AUC<sub>insulin</sub> than the other diets (**Figure 3**). In contrast, dogs fed the barley diet had the lowest average postprandial plasma insulin levels and AUC<sub>insulin</sub> compared with the other starches. The dogs fed corn had a relatively low average postprandial glucose response and AUC<sub>glucose</sub> but resulted in intermediate insulin responses. These studies indicate that diets for improving glycemic control in dogs could contain barley, corn and/or sorghum. Conversely, rice is contraindicated as a starch source for animals with poor glycemic control.

In cats, the normal glycemic response is substantially longer than that of dogs and humans.<sup>51</sup> While a typical glycemic response lasts 4 to 6 hours in dogs, glucose and



**Figure 2.** 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 3.** 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.)

insulin levels in cats are elevated for 18 hours or more before returning to baseline levels. In the study described above, patterns of glucose response differed with starch source.<sup>50</sup> Cats fed rice had significantly higher glucose levels two hours after feeding compared with cats fed wheat, barley or corn. Overall, rice and sorghum caused relatively rapid increases in blood glucose compared with the other starches. The glucose response in cats fed rice declined rapidly following the peak, while glucose levels in cats fed sorghum declined gradually. Conversely, wheat and barley resulted in a sustained postprandial glucose increase, a delayed glucose peak, and a rapid decline following the peak. Corn had an intermediate glucose response. Similar to dogs, overall glycemic response (glucose and insulin) was exacerbated when cats were fed rice as the primary carbohydrate source. Comparatively, barley, corn and sorghum produced varying effects on postprandial glucose, but stimulated relatively low postprandial insulin responses. These results suggest that barley, corn and/or sorghum are beneficial in improving glycemic control.

A recent study compared the effects of feeding overweight cats a diet formulated with starches to enhance glycemic control (sorghum and corn) with a diet containing rice as its primary starch.<sup>52</sup> Meal response and glucose tolerance tests were conducted before and after a 6-week weight maintenance phase and after a subsequent 8-week ad libitum feeding phase. During the ad libitum phase of the study, cats fed the rice-containing diet had significantly higher food intakes and gained significantly more weight than cats fed the sorghum/corn diet. Cats fed the rice diet also had increased glucose responses after a test meal and this effect was exacerbated by ad libitum feeding. Feeding rice increased peak glucose concentrations, AUC<sub>glucose</sub> and

average glucose concentration when compared with the sorghum/corn diet. After being allowed free access to food, measures of glucose control were negatively influenced in cats fed the rice diet but remained unchanged in cats fed the sorghum/corn diet. Although not statistically significant, insulin concentration and its derived indices tended to be higher in cats fed the rice diet following a test meal or in response to a glucose challenge. These results support the evidence that a sorghum and corn starch blend enhances glycemic control in overweight cats, and also suggests that weight gain associated with free-choice feeding a rice-containing diet can compound the negative effects that rice has upon glycemic response.

## Fiber

Diets containing certain fibers at moderate levels can improve glycemic control by either slowing the rate of carbohydrate absorption, altering secretion of gastrointestinal hormones that control nutrient metabolism, and/or improving the timing of insulin release. Some viscous fibers, such as carboxymethylcellulose, form a gel layer that slows the convective transfer of glucose and water to the absorptive surface of the intestine, thereby delaying or dampening the postprandial glucose response.<sup>53</sup> Fermentable fibers may also enhance glucose metabolism through effects on insulin. There is recent evidence that the short-chain fatty acids (SCFA) generated from fermentable fibers by intestinal bacteria stimulate the release of a compound called proglucagon by cells of the intestinal mucosa.<sup>54</sup> Proglucagon is a precursor of glucagon-like peptide-1 (GLP-1), which in turn enhances the secretion of insulin from pancreatic beta cells during periods of elevated blood glucose.<sup>55</sup>

A study was conducted to compare the influence of a fermentable fiber blend (beet pulp, gum arabic and fructooligosaccharides) to a nonfermentable fiber (cellulose) on glucose homeostasis in dogs.<sup>56</sup> Sixteen dogs were randomly assigned to one of the two experimental diets. Oral glucose tolerance tests were performed at the end of a two-week feeding period. Feeding the fermentable fiber blend resulted in significantly increased production of intestinal proglucagon mRNA, higher incremental GLP-1 and insulin secretion, and improved glucose tolerance. The incremental AUC<sub>glucose</sub> was also lower in dogs who consumed the fermentable fiber diet and this was associated with the increase in GLP-1 response. Because increased GLP-1 is associated with improving glucose tolerance during periods of elevated blood glucose, providing a fermentable fiber blend may aid in normalizing glucose control by improving the timing and effects of insulin release.

## Chromium

The essential trace mineral chromium is required for normal carbohydrate and lipid metabolism.<sup>57-59</sup> Although its mode of action is not completely understood, the bio-



logically active form of chromium improves glucose metabolism by potentiating the action of insulin. Chromium is an integral component of glucose tolerance factor, which also contains nicotinic acid, glutamic acid, glycine and cysteine.<sup>60</sup> In humans, a deficiency of chromium is associated with abnormal glucose utilization and insulin resistance, and chromium supplementation has been shown to improve glycemic control in obese and diabetic patients.<sup>61</sup> Chromium supplementation has also been shown to increase glucose uptake by tissues in swine and cattle.<sup>62,63</sup> These results suggest that chromium supplementation may have a role in improving glycemic control in dogs and cats. Until recently, studies of the glucose-regulating effects of chromium in dogs and cats had not been conducted.

A set of experiments examined the effect of chromium supplementation on glucose metabolism and insulin sensitivity in healthy adult dogs.<sup>64</sup> In two experiments, groups of 24 Beagles were fed diets formulated to contain 0, 150, 300 or 600 ppb of chromium tripicolinate. When challenged with an intravenous glucose dose, dogs that received supplemental chromium had lower plasma glucose concentrations for 30 minutes and slightly higher glucose clearance rates between 10 and 30 minutes compared with control dogs. Dogs that were supplemented with 300 ppb chromium had a 10 % faster clearance rate of glucose ( $P < .08$ ) compared with unsupplemented dogs. Chromium supplementation also was associated with lower fasting blood glucose levels, but did not affect serum insulin responses. These results are consistent with those reported in humans and other species, and suggest that chromium supplementation in dogs increases tissue sensitivity to the effects of insulin.

Similar results are reported in cats. A recent study examined the effects of supplemental chromium tripicolinate on healthy, non-obese cats.<sup>65</sup> Thirty-two cats were randomly assigned to one of four standard diets to which either 0, 150, 300 or 600 ppb of chromium tripicolinate was supplemented each day. Cats were fed their assigned diet for a period of 6 weeks, and pre- and post-test glucose tolerance, insulin tolerance, and insulin sensitivity tests were performed. Supplementation with 300 and 600 ppb chromium tripicolinate resulted in significantly lower glucose concentrations and  $AUC_{\text{glucose}}$  during the glucose tolerance test. Supplementation with 300 ppb also significantly reduced the half-life of glucose in the blood, while supplementation with 600 ppb significantly reduced fasting glucose levels. The improvements that were seen in glucose tolerance in these cats were small, but were statistically significant and were dose-dependent. Together, the results of these two studies suggest that increasing the level of chromium in diets formulated for pets with poor glycemic control may enhance tissue sensitivity to insulin.

### Leptin and Vitamin A

Leptin is a hormone secreted by white adipose tissue that has a role in regulating adiposity, food intake, and

energy expenditure.<sup>66</sup> The concentration of leptin in the blood is positively correlated with the amount of body fat and appears to be one of the signal molecules that indicates the size of fat depots in the body.<sup>67</sup> Increases in leptin concentrations have also been correlated with insulin resistance in lean and obese humans.<sup>68,69</sup> It has been theorized that one of the mechanisms by which increased adiposity leads to insulin resistance and increased risk of DM may be through the action of leptin.<sup>70</sup> Although more evidence of a causal relationship is needed, *in vitro* studies have shown that leptin affects the ability of tissues to respond to insulin.<sup>71</sup> There is also evidence that leptin may directly influence the secretion of insulin from pancreatic beta cells.<sup>72</sup>

A recent study with 16 cats measured serum leptin concentrations during a series of glucose tolerance tests conducted before and after weight gain.<sup>73</sup> Results showed that cats with higher leptin concentrations were also more insulin resistant, and this relationship occurred in both lean and overweight cats. Overall, leptin concentrations before and after consuming a test meal tended to be higher in overweight cats who were glucose intolerant compared with overweight cats who exhibited normal glucose tolerance. The results of this study suggest that increased leptin concentrations may either be a precipitating agent in the diminished insulin sensitivity associated with weight gain, or could be secreted in response to the hyperinsulinemia that occurs in overweight cats. It is possible that serum leptin levels can provide an accurate marker for predicting insulin insensitivity in susceptible cats.

Modifying leptin levels through diet may be an approach to help modulate insulin sensitivity in susceptible animals. There is evidence that retinoic acid, a derivative of vitamin A, decreases the expression of leptin mRNA in white adipose tissue.<sup>74</sup> Moreover, providing supplemental vitamin A has been shown to suppress leptin gene expression and lower serum leptin levels.<sup>75,76</sup> When dogs and cats were fed unrestricted amounts of a high-fat, energy-dense diet formulated with or without supplemental vitamin A, those receiving supplemental vitamin A had significantly reduced serum leptin levels.<sup>77</sup> Including supplemental vitamin A or other nutrients that help to normalize serum leptin levels may provide an adjunct approach for improving insulin sensitivity.

### Feeding Regimen

Feeding several small meals, spaced evenly throughout the day, has traditionally been the recommended schedule for dogs and cats with impaired glycemic control or DM. The intent of this approach is to minimize glucose fluctuations and optimize glycemic control. This schedule is especially desirable for many cats and their owners as consuming numerous small meals per day is the natural feeding pattern of the domestic cat. A study was recently conducted to determine the effects of *ad libitum* feeding vs. meal feeding (one meal per day) upon glycemic control in cats.<sup>78</sup> For the

ad libitum test, the cats were allowed free access to their food prior to and during a 12-hour simplified glucose tolerance test. For the meal response test, cats consumed more than 90% of their previous 12-hour ad libitum intake within a 30-minute meal period. Results showed that mean insulin concentration was 40% higher in response to ad libitum feeding compared with meal feeding. Interestingly, no differences were seen in mean glucose concentration between the two feeding regimens, but glucose concentrations were lower for the meal response test at time 0 (start of the test) and higher 6 hours post-feeding, compared with the ad libitum test. These results suggest that ad libitum feeding (numerous small meals per day) results in significantly higher insulin concentrations compared with providing a single daily meal in cats. Over time, this may result in an increased demand on the pancreatic beta cells and may contribute to hyperinsulinemia and beta cell exhaustion.

## CONCLUSION

A nutritional approach to controlling glycemia and treating diabetes mellitus in dogs and cats includes diets formulated to contain lower levels of fat that promote normalization of the pet's glycemic response. Other nutrients that may increase efficiency of glucose metabolism and help to reduce insulin resistance include certain types of starch and fiber, chromium, and vitamin A. Consideration of the feeding regimen used with susceptible cats may also be important.

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# Nutritional Management of Weight in Dogs and Cats

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## INTRODUCTION

Obesity is the most common nutritional disease seen in companion dogs and cats today. It is estimated that between 25 and 44% of dogs and between 20 and 35% of cats are overweight or obese.<sup>1-4</sup> Overweight conditions are most simply defined as the accumulation of excessive fat in adipose tissue in the body.<sup>5</sup> Although a pet's body weight (BW) alone may not always provide a definitive diagnosis of obesity, companion animals are generally considered to be overweight when their mature weight exceeds ideal BW by 5% or more, and obese when their weight exceeds ideal BW by 15 to 20%.

<sup>†</sup> Deceased.

Overweight and obese conditions are associated with the development of a myriad of health problems. Obese dogs are at increased risk of developing hypertension, osteoarthritis, mammary tumors, elevated blood triglycerides, and pancreatitis.<sup>6-10</sup> In both dogs and cats, aberrations in normal glucose metabolism and homeostasis occur with obesity. Overweight dogs are more likely to be insulin resistant, hyperinsulinemic and glucose intolerant.<sup>11-13</sup> Likewise, obese cats often develop glucose intolerance and insulin resistance, which can lead to a form of diabetes analogous to type 2 diabetes in humans.<sup>14-16</sup> Obese cats also are at increased risk for hepatic lipidosis, increased blood triglycerides, and feline lower urinary tract disease compared with normal weight cats.<sup>17-19</sup>

## CAUSES AND RISK FACTORS

The underlying fundamental cause of obesity is a chronic imbalance of energy, with intake exceeding expenditure. Over time, even a relatively small daily energy surplus will lead to gradual weight gain and obesity. A number of risk factors have been shown to contribute to obesity in companion animals. These include neutering, being middle-aged, inactivity, a confined lifestyle, and genetic (breed) predispositions.<sup>20,21</sup> The relationship between owners and their pets also plays an important role. For example, owners of overweight dogs are more likely to be overweight themselves, and they are more inclined to interpret all of their dog's needs as requests for food when compared with normal weight owners.<sup>22</sup> Feeding dogs excessive amounts of highly palatable treats, human foods or table scraps also can contribute to the development of obesity, as can competition for food in multiple dog households.<sup>23-25</sup> The human-cat relationship also must be considered. Cats who are perceived by their owners to be close and important family members or child substitutes are more likely to be obese than those cats whose presence in the home is merely tolerated or are considered to be only playmates.<sup>26</sup>

## DIAGNOSIS

Accurate diagnosis of obesity is important for devising a treatment plan and achieving optimal weight loss for the animal companion. Comparing current BW to an estimate of ideal BW is a helpful starting point. Ideal BW can be estimated through a physical examination of the animal, obtaining information from the owner, and from medical records of the pet's weight shortly after attaining mature weight. The use of Body Condition Score (BCS) protocols

provides an additional assessment of body fat and condition. BCS takes into account skeletal frame size and physical assessments of subcutaneous and abdominal fat deposits, and has been shown to provide a reliable method for diagnosis of obesity.<sup>27,28</sup> Comparisons of body composition data collected using dual energy x-ray absorptiometry (DEXA) with assessments using a BCS system have revealed significant and positive correlations between BCS and percent body fat in dogs and cats. In addition to these diagnostic tools, subjective evaluation of the animal's gait, exercise tolerance, and overall appearance can be used to support a diagnosis of obesity.

## TRADITIONAL WEIGHT LOSS APPROACHES

The complexity of treating obesity in dogs and cats is often disregarded because the solution appears to be very simple—one just decreases the pet's food portion size. Indeed, if it were that simple, veterinarians, breeders and pet owners would be markedly more successful in preventing and treating obesity in companion animals. Because many pets are refractory to treatment, and because multiple factors contribute to the development and the maintenance of obesity, an effective treatment plan is multifaceted. It must include a food that provides nourishment and satiety while causing effective and safe losses of adipose tissue, as well as behavioral approaches that encourage owner compliance and commitment.

Traditionally, many feline and canine diets formulated for weight loss have contained high amounts (10 to 20%) of crude fiber. Measured as total dietary fiber, this level of crude fiber is equivalent to between 20 and 40% dietary fiber.<sup>29</sup> The purported benefit of these products is that the increased bulk, reduced caloric density, and decreased digestibility of a high-fiber diet will contribute to satiety and cause a decrease in voluntary energy intake. However, data available indicate conflicting results for the role of fiber on food consumption and weight loss in dogs.<sup>30-33</sup> Concerns also exist in that feeding excessive fiber may produce adverse side effects such as decreased nutrient digestibility, increased defecation frequency, and stool production, poor skin and hair coat quality, and poor diet palatability and acceptance.<sup>34-36</sup>

## NEW APPROACH TO WEIGHT LOSS MANAGEMENT

A new paradigm for the nutritional management of weight addresses the specific physiological and metabolic changes associated with weight gain in companion animals. A successful treatment program addresses the physiological changes associated with obesity and with weight loss, as well as the underlying reasons for overfeeding and overeating. An appropriate diet for weight loss for dogs and cats is one that has normal levels of fiber, provides adequate protein, is low in fat and has reduced caloric density. Adequate

protein is especially important for cats because compromised protein intake during weight loss has been identified as a possible factor in the development of feline idiopathic hepatic lipidosis.<sup>37</sup> In addition to these general nutritional guidelines, select nutrients are included at appropriate levels to help to normalize the metabolic, physiologic and health alterations that are seen in overweight animals.

Most nutritionists and clinicians agree that safe weight loss ranges between 1.0 and 2.5% of current (overweight) BW per week. A slower rate of loss can be discouraging to owners, while rapid weight losses can result in excessive losses of lean body mass (LBM). Rapid weight loss is specifically contraindicated in cats due to the risk of developing hepatic lipidosis. Generally, it is reasonable to attempt to achieve a loss of 20 to 25% of BW over an 18-week period (provided the animal was already over weight). A primary goal during obesity treatment is to minimize lean tissue losses while allowing for safe adipose tissue loss. Since adipose tissue is less metabolically active than lean body tissue, maintaining LBM throughout weight loss aids in preventing a concomitant decrease in resting energy requirement (RER). Increasing the pet's activity and exercise as part of a weight management program also helps to offset losses of LBM and to maintain body condition and RER.

Finally, weight loss programs for companion animals must address owner motivation and commitment to encourage compliance and ultimate success. Because it is the owner who ultimately controls the amount and type of food that is provided and the level of exercise that a pet receives, the owner's role in weight loss and weight management for dogs and cats cannot be undervalued.

## NORMALIZING GLYCEMIC RESPONSE

Glucose intolerance and diabetes are associated with overweight conditions in dogs and cats. For example, a

study comparing 35 obese dogs to 20 dogs of normal weight found that the overweight dogs were more likely to be glucose intolerant and to experience hyperinsulinemia compared with normal dogs.<sup>38</sup> A similar relationship occurs in cats. Cats that weigh 20% or more above ideal BW have increased baseline glucose levels and peak glucose and insulin levels in response to an intravenous glucose tolerance test.<sup>39</sup> Obese cats also are at increased risk of developing insulin resistance. Providing a food that normalizes postprandial glucose and insulin responses is expected to be beneficial in correcting impairments in glucose control during weight loss. Several nutrients are helpful in achieving this goal.

**Starch.** Starch is the principal source of carbohydrate and an important source of energy in dog and cat diets. Types of starch vary significantly in their postprandial glycemic effects. A study of the glycemic responses of dogs fed diets containing 30% starch supplied as either corn, wheat, barley, rice or sorghum showed that the highest postprandial glycemic and insulin responses occurred when rice was fed.<sup>40</sup> In comparison, feeding sorghum resulted in the lowest postprandial glucose response, and feeding barley resulted in comparatively lower postprandial insulin responses. Similar results were reported in a study of senior dogs fed different starch sources.<sup>41</sup> Overall, because barley, sorghum, and corn result in more moderate glucose and insulin responses, these starches are recommended for weight loss diets.

In cats, the normal glycemic response is substantially longer than that seen in dogs and humans.<sup>42</sup> While a typical glycemic response lasts 4 to 6 hours in dogs, glucose and insulin levels in cats are elevated for 18 hours or more before returning to baseline levels. Similar to dogs, overall glycemic response (glucose and insulin) is exacerbated when cats are fed rice as a primary carbohydrate source.<sup>43</sup> Comparatively, barley, corn, and sorghum produce varying effects on postprandial glucose, but stimulate relatively low postprandial insulin responses. These results suggest that a combination of barley, corn or sorghum is beneficial as a primary source of starch for cats with impaired glucose control.

**Selected Fibers.** Improving glycemic control in overweight dogs and cats can also be achieved by including low to moderate amounts of select types of fibers in the diet. Examples of fermentable fibers include beet pulp, fructooligosaccharide, and gum arabic. Fermentable fibers, unlike the nonfermentable dietary fibers traditionally included in weight loss diets, can dampen the postprandial glycemic response and enhance glycemic control. Fibers that are also viscous may slow gastric emptying and form a gel layer that slows the convective transfer of glucose and water to the absorptive surface of the intestine. Feeding of the soluble fiber carboxymethylcellulose at 1% of the diet

was shown to decrease postprandial glycemic responses in normal healthy dogs.<sup>44</sup> Thus, careful selection of fibers may improve glycemic control by slowing the rate of absorption of digestible carbohydrates, altering the secretion of gastrointestinal hormones that control nutrient metabolism, improving the timing of insulin release, or a combination of these factors.

Diets containing fermentable fiber also can improve glucose metabolism through effects of the short-chain fatty acids (SCFA) that are generated from fermentable fibers by intestinal bacteria. Short-chain fatty acids have been shown to stimulate the release of a compound called proglucagon by cells of the intestinal mucosa.<sup>45</sup> Proglucagon is a precursor of glucagon-like peptide-1 (GLP-1), which in turn enhances secretion of insulin from pancreatic beta cells during periods of elevated blood glucose. Studies with healthy dogs have shown that feeding a diet containing a moderately fermentable fiber mixture increased production of GLP-1 and insulin secretion and decreased blood glucose response to an oral glucose load.<sup>46</sup> This enhancement of glycemic control may contribute to the normalization of blood glucose and insulin levels of overweight or obese pets.

A recent study was conducted with overweight dogs to determine whether a diet formulated for both weight loss and glycemic control would more effectively promote weight loss than a traditional high-fiber, weight-loss diet.<sup>47</sup> Dogs fed each of the diets lost weight, but those fed the glycemic-control diet lost 50% more body fat, had higher percentages of LBM, and showed improved measures of glucose metabolism compared with dogs fed the high-fiber diet.

**Chromium.** Including supplemental chromium tripicolinate in the diet can improve blood glucose clearance in dogs and improve glucose tolerance in normal and obese cats.<sup>48-50</sup> The mechanism through which chromium influences glucose metabolism appears to be related to its effects on insulin. Chromium potentiates the action of insulin by enhancing the binding of insulin to cells and by increasing the number of insulin receptors on cell surfaces. Chromium also improves insulin sensitivity by increasing insulin receptor phosphorylation. In addition to its influences on glucose homeostasis, chromium also appears to contribute to improved body condition during weight loss. When 36 ovariectomized cats were fed 0, 300 or 600 ppb of chromium tripicolinate during weight loss, cats fed supplemental chromium preserved higher proportions of LBM compared with cats who were not supplemented.<sup>51</sup> During the weight loss period, all of the cats lost weight, but the supplemented cats lost more fat and less lean tissue compared with the non-supplemented cats. Since an important goal of all weight loss programs is to prevent lean body mass while losing fat tissue, including chromium in diet formulations for treating obesity appears to be beneficial.

## PROMOTING NORMAL FAT METABOLISM AND IMPROVING BODY CONDITION

Overweight dogs and cats have an increased risk for elevated triglyceride and very-low-density lipoprotein levels compared with normal weight animals.<sup>52,53</sup> Effective weight loss diets should be formulated to enhance fat metabolism and to modulate serum lipid levels.

**Dietary Fat.** Recent studies have evaluated the efficacy of feeding low-fat, low-fiber diets to overweight and obese cats for the purpose of weight reduction.<sup>54,55</sup> When pet cats who were up to 40% overweight were fed a low-fiber, moderate-fat, reducing diet to provide 60% of their calculated energy requirement, all cats lost significant amounts of weight and more than half reached 90% of ideal body weight within 18 weeks. In a subsequent study, a group of obese cats were fed a low-fat, low-fiber diet restricted to intakes that were calculated to achieve 1.5% body weight loss over a 16-week period. Cats lost an average of 21% of their body weight and 49% of their body fat. DEXA body composition analysis showed that LBM decreased only slightly. This resulted in mean final body conditions that were lower in fat tissue and higher in lean tissue. These studies demonstrate that decreasing the fat level of a weight management diet can promote safe weight loss while preventing excessive losses of LBM.

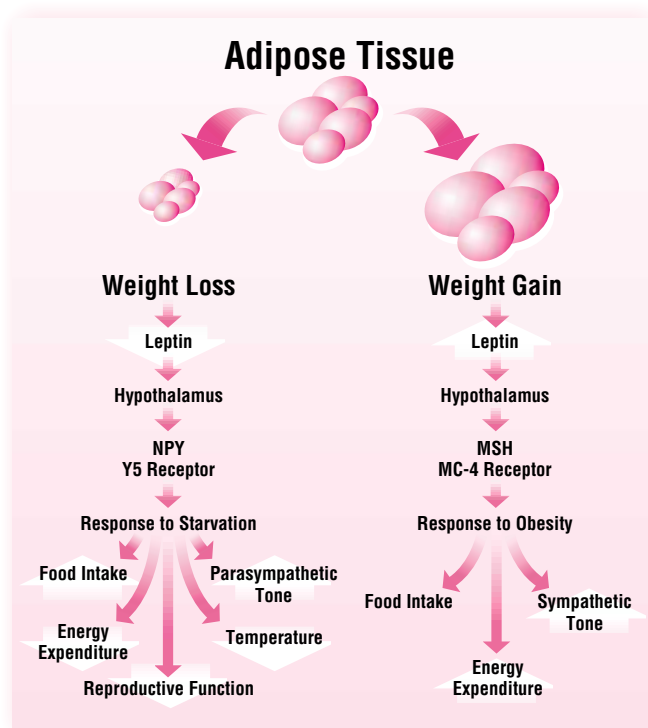
The amino acids methionine and arginine have been suggested to precipitate hepatic lipidosis in obese, energy restricted cats.<sup>37</sup> However, overweight cats can rapidly lose weight without the side effect of overt hepatic lipidosis when fed a diet containing both high-quality protein and long-chain fatty acids (arachidonic acid [20:4n6] and, possibly, docosahexanoic acid [20:6n3]).<sup>56</sup> These results indicate that the type (source) of fat as well as protein is important to healthy weight loss in cats.

**Carnitine.** L-Carnitine is a vitamin-like compound that promotes fatty acid metabolism. It is a component of the enzyme system carnitine palmitoyl transferase that transports fatty acids into mitochondria for beta oxidation. Studies with dogs and cats have demonstrated enhanced weight loss and increased loss of fat mass in animals supplemented with L-carnitine compared with animals who were not supplemented.<sup>57,58</sup> In dogs, adding supplemental carnitine to the diet appears to also help to control appetite, without affecting diet palatability.<sup>59</sup> Of special interest to companion animals are studies showing that the inclusion of L-carnitine in the diets for cats undergoing rapid weight loss can attenuate the metabolic and hepatic histopathic changes that are associated with the development of hepatic lipidosis.<sup>60</sup>

## ADDRESSING HORMONAL ALTERATIONS

Elevated blood levels of the hormone leptin is another physiological alteration that occurs with overweight conditions. Leptin is a 16kDa protein secreted by

white adipose tissue that has a role in regulating the degree of adiposity in an individual (**Figure 1**). Leptin level in the blood is positively correlated with the amount of body fat and appears to be one of the signal molecules that indicate the size of fat deposits in the body.<sup>61</sup> Dietary manipulation of leptin levels may be important for the control and management of obesity.



**Figure 1.** The biological response to leptin. Adapted from Friedman JM. Leptin, leptin receptors, and the control of body weight. *Nutr Rev* 1998; 56:S38-S46. (Abbreviations: NPY= neuropeptide; MSH=melanocyte-stimulating hormone; MC-4=melanocortin-4).

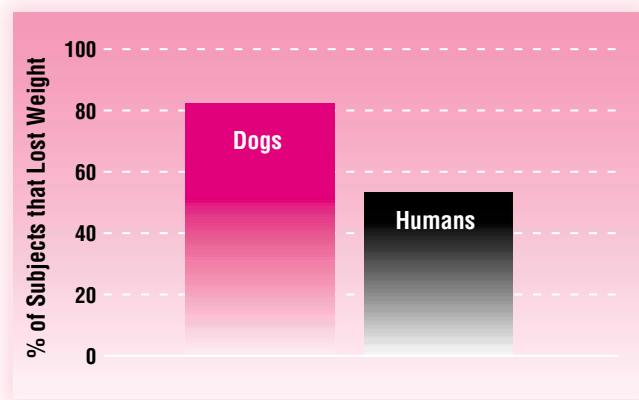
**Vitamin A.** There is evidence that retinoic acid, a derivative of vitamin A, decreases the expression of leptin mRNA in white adipose tissue.<sup>62</sup> Providing supplemental vitamin A has been shown to suppress leptin gene expression and lower serum leptin levels.<sup>63,64</sup> Studies of dogs and cats fed diets containing increased vitamin A levels found that when animals were fed unrestricted amounts of a high-fat, energy-dense diet, those receiving extra vitamin A gained less weight than did the unsupplemented animals.<sup>65</sup> Including supplemental vitamin A in weight loss formulations for dogs and cats may be helpful in promoting the normalization of serum leptin and in ultimately improving weight management.

## PRACTICAL CONSIDERATIONS: THE HUMAN-PET RELATIONSHIP

The relationship between owners and their pets plays an important role in the development of overweight condi-

tions and in the treatment of obesity. Obesity is currently an important health issue for both companion animals and their human caretakers. It is estimated that up to 60% of adult humans in the United States are overweight, and overweight owners are more likely to have obese dogs. Weight management programs must address this relationship and should include an approach that promotes client motivation and long-term compliance.

One novel approach is to suggest a shared exercise and healthy eating plan for overweight owners and pets. This “partnering” approach may provide the motivation and commitment that is needed for success. A pilot study was conducted to test whether families with an overweight primary caregiver and an overweight dog would benefit from a 6-month, joint-healthy, eating, weight loss and exercise program.<sup>66</sup> Participants were provided with diet information (human and pet), a weight loss diet for the dog, and education regarding healthy eating, exercise, and a healthy lifestyle. Over the 6-month period, 82% of the dogs lost weight and more than half (55%) of the human caretakers lost weight (**Figure 2**). Dogs that lost weight had a mean weight reduction of 10%. Daily diaries and questionnaires indicated that the owners’ believed their dogs to be experiencing improved quality of life and overall health, and increased energy levels. Correlative human behavior changes included improved eating habits, substantial increases in exercise frequency and duration, and increased number of interactions (walking) with their dog. The results of this pilot study indicate that addressing the human-pet relationship may enhance compliance and improve success in weight loss programs for companion animals.



**Figure 2.** Human-animal partnership for weight loss. (Murray, 2002)

## CONCLUSION

New and innovative approaches to weight management diets for dogs and cats include the use of reduced fat diets that contain normal levels of appropriate fiber sources, in contrast to traditional diets that contained excessive levels of non-fermentable fiber. In addition, the inclusion of novel weight-modulating nutrients, such as certain starches,

chromium, l-carnitine and vitamin A, addresses the physiological and metabolic alterations associated with obesity. Diets formulated for weight loss that contain these nutrients are demonstrated to enhance weight loss and control, while preserving LBM and promoting health.

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# Clinical Weight Management for Dogs and Cats

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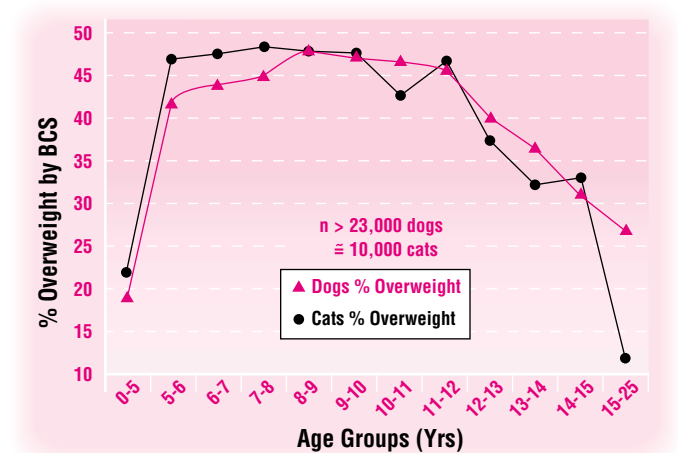
## INTRODUCTION

Obesity is the most common and costly nutritional problem in human health care in North America. Exceeding ideal body weight (IBW) has also recently been acknowledged to be a common problem plaguing human health in European and Middle Eastern countries. Companion animals appear to have a similar problem as obesity is recognized as the most common nutritionally related health problem in pet dogs and cats. Long-term weight management of the obese pet can present a frustrating clinical challenge destined for failure unless an organized approach with practical strategies are adopted.

## ESTIMATED INCIDENCE OF OBESITY

Studies estimate the incidence of overweight and obese cats to range between 19 and 40% and of overweight or obese dogs to range between 24 to 45%.<sup>1-10</sup>

In 1973, a survey conducted in the United Kingdom reported an incidence of over-conditioned cats to range between 6–12% of those seen in veterinary practices.<sup>1</sup> In 1992, a prevalence of 40% was reported for over-conditioned cats in Europe.<sup>2</sup> In 1994, approximately 25% of over 2,000 cats examined in 31 private veterinary practices in North America were considered overweight (20%) or obese (5%) with highest risk in cats between 6 and 8 years of age.<sup>3</sup> In that same year, based on 1,600 cats examined at the University of Pennsylvania, an overweight body condition in adult cats was most common between 4 and 6 years of age.<sup>4</sup> In 1996, a study of nearly 10,000 cats in 60 veterinary practices in North America determined that 24% of cats exceeded optimal body weight (body condition score [BCS] of 4 or 5 using a 5-point scale), with highest risk between 5 and 12 years of age and peak incidence at 7 years of age (nearly 50% of cats examined); **Figure 1.**<sup>5</sup>



**Figure 1.** Findings from a survey of body condition scores in dogs and cats in 60 veterinary practices in North America; 5-point body condition score, score of 4 or 5 indicating overweight and obese animals, respectively. Adapted from reference 5.

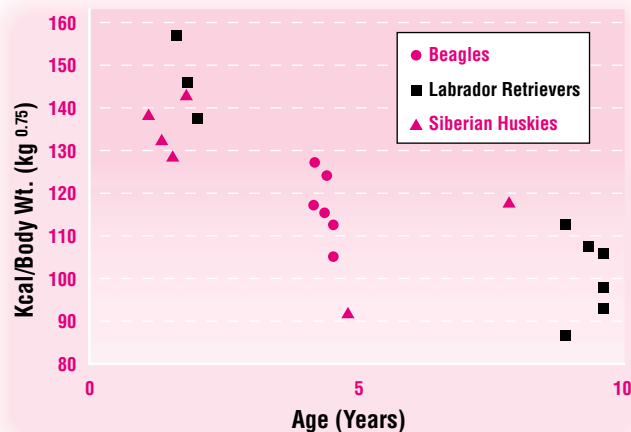
Studies confirm that middle-aged and older dogs have increased risk for becoming over-conditioned. In 1970, Mason's survey of 1,000 dogs at a veterinary clinic in the United Kingdom reported a relationship between age and over-conditioning.<sup>6</sup> An overweight body condition in dogs of various ages was found in 16.5% in dogs < 4 years, 35.5% in dogs 5–11 years, and 40.5% in dogs > 12 years.<sup>6</sup> In 1991, a survey of 3,729 dogs at the University of Pennsylvania found that nearly 28% of dogs ranging in age from 7–9 years were overweight.<sup>7</sup> In 1996, a survey of over 23,000 dogs completed in 60 different veterinary practices in North America disclosed a 25% prevalence of overweight/obese dogs (BCS of 4 or 5 on a 5-point scale).<sup>5</sup> Approximately

40–45% of dogs between 5 and 12 years of age had a BCS of 4 or 5; **Figure 1**.<sup>5</sup> After 12 years of age, the prevalence of over-conditioned animals declined, consistent with the age related loss of lean body mass (LBM), mostly comprised of muscle, and reduced activity shown by others investigating energy requirements in aging dogs; **Figure 2**.<sup>8-16</sup> As early as 1980, body composition studies in adult dogs reported mean body fat at 1 year of age of 15–20% and that this increases continually in successive years reaching 25–30% in dogs aged 8 to 10 years.<sup>16</sup> This and other work in aging dogs substantiates an age-related decline in LBM.<sup>16</sup>

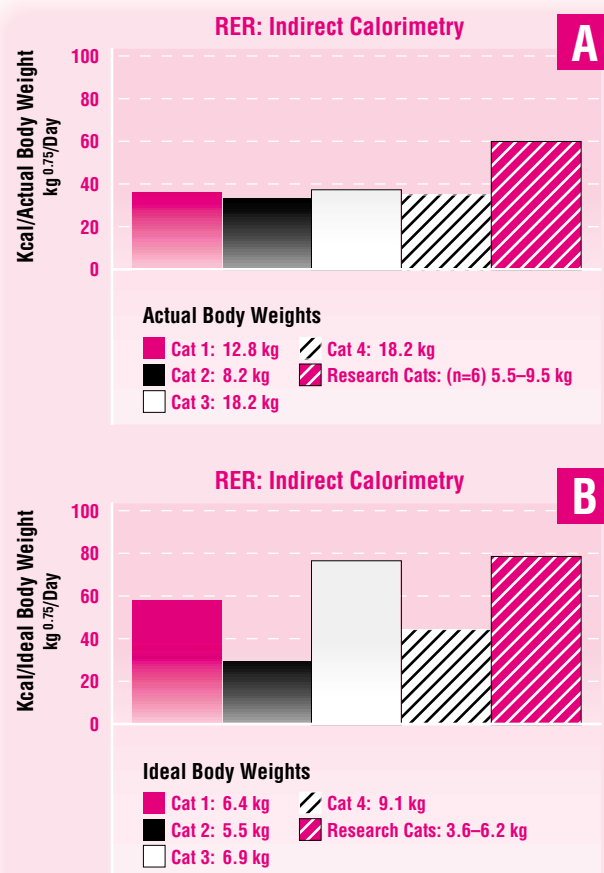
## ETIOLOGY OF OBESITY

Obesity is an insidious pathological condition having a multifactorial etiology. Abnormally low metabolic rates derived from genetic or acquired disorders have been shown in some obese humans. Similar phenomena may exist in some animals; examples of abnormally low resting energy requirement (RER) for several morbidly obese pet cats are displayed in **Figure 3**. Other factors that may favor obesity include abnormalities in satiety and appetite control mechanisms, psychological factors causing hyperphagia, expansion in number or size of adipocytes, impaired ability or desire to exercise, and simply, consistent over-feeding of a palatable food exceeding the daily energy requirement (DER). There is also evidence that obesity influences skeletal muscle metabolism, not only related to insulin resistance in pathways of glucose metabolism, but also in respect to reduced utilization of fat calories.<sup>17</sup> Such effects on muscle are important since it is here that the largest component of LBM is partitioned and where > 95% of metabolic activity or energy utilization occurs.<sup>18</sup>

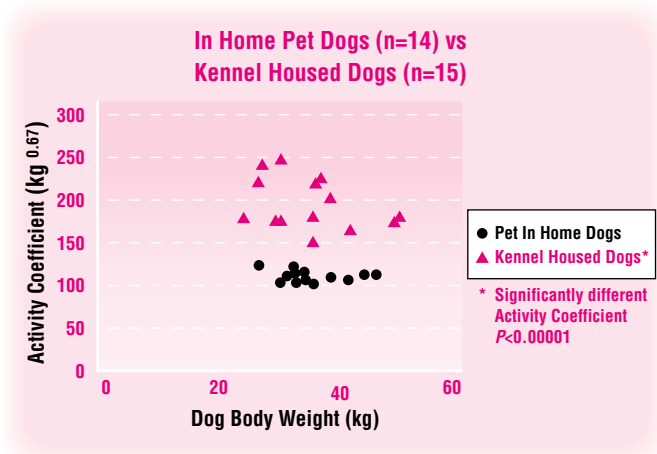
Overfeeding of pet dogs has been unintentionally fostered by National Research Council (NRC) recommendations (1974 & 1985), which influence feeding guidelines suggested by pet food manufacturers, veterinary nutritionists, and veterinarians.<sup>19,20</sup> Recent studies have highlighted differences between daily or maintenance energy requirements (DER or maintenance energy requirement [MER], depending on the study) for kennel-housed research dogs (which serve as the basis for NRC recommendations) and in-home pet dogs; some of this data is illustrated in **Figure 4**.<sup>21-25</sup> The DER represents the average daily energy expenditure dependent on lifestage and activity, differing from MER as it includes extra energy required for activity or work, gestation, lactation, growth, and for maintenance of normal body temperature (when the animal is not maintained in a thermoneutral environment). For many studies the DER equals the MER; hereafter the term DER will be used unless specifically indicated otherwise. The range of activity factors (factor multiplied with estimated RER) required to achieve stable body weight in the in-home pet dog (data derived from 4 recent studies involving more than 200 in-home pet dogs) supports the notion that many animals require con-



**Figure 2.** Effect of age on energy requirements for maintenance of stable body weight in kennel-housed dogs (3 different pure breeds); adapted from reference 15.



**Figure 3.** Resting energy requirements (RER) determined by indirect calorimetry for 4 morbidly obese pet cats (% ideal body weight = 150–200%) and 5 colony-housed research cats “fattened” for obesity studies (average % ideal body weight = 135%). The RER expressed per kg<sup>0.75</sup> for actual body weight (graph A) and estimated ideal body weight (graph B) are shown. Pet cats 2 and 4 have a significantly lower RER compared to values for research cats and most pet cats studied in our laboratory.



**Figure 4.** Maintenance energy requirements at stable body weight for in-home pet dogs and kennel-housed dogs of comparable body size. In-home pet dogs have a significantly lower daily energy requirement compared to kennel housed research dogs. The activity coefficient of in-home pet dogs averaged 59% of kennel-housed dogs.

servatively from 15 to 36% less energy than predicted from NRC<sup>19,20</sup> recommendations. (It should be noted that a number of in-home dogs have been shown to require even less energy.<sup>24</sup>)

Measurement of RER in pet dogs using indirect calorimetry suggests that differences in DER between in-home pet dogs and kennel-housed dogs is likely due to higher physical activity in the latter animals.<sup>25</sup> This is deduced by comparing ingested energy of in-home pet dogs and calculating the activity factor for each individual (factor times RER determined by indirect calorimetry).

The reality of a lower activity level in many in-home pet dogs compared to “working” dogs has been well demonstrated with data collected on Border Collies.<sup>26</sup> In that report (40 pet and 28 working dogs), the majority of pet dogs (87.5%) received either < 1 hour or between 1 and 3 hours of daily exercise.<sup>26</sup> While it is conventional to define the activity level of an individual when calculating their DER, this estimate is difficult and remains poorly defined. Further, owners or veterinarians may not realistically or accurately describe a pet’s activity. While pet owners may consider that their dog is an athlete or athletic, small bursts of energy (eg, barking at occasional house guests, short walks of 30 minutes or less, access via dog door to a fenced yard) do not constitute circumstances causing moderate or high energy utilization. Further, it is important to remember that only a relatively small positive energy balance (energy intake exceeding DER) is sufficient to result in weight gain over time. In addition, two dogs of equal size with the same BCS in the same environment with the same visible activity can have disparate DER.

A good example to consider is what occurs in humans where it is estimated that daily ingestion of only 0.3% excess energy explains the insidious accumulation of an

average of 9 kg extra weight between the ages of 25 and 55 years.<sup>27</sup> Furthermore, in man, if energy intake exceeds DER by only 5% each day, a 5 kg fat mass accrues over one year, and morbid obesity over several years.<sup>28</sup> Unfortunately, the small difference of 5% between energy intake and expenditure is barely measurable clinically, complicating detection of this imbalance in short-term studies.<sup>28</sup>

The other factor contributing to the difference in DER of in-home pet dogs compared to commonly used NRC guidelines is the neutered status of many pets. Neutering is proposed by some to reduce the metabolic rate, to influence animal activity (reducing social interactions/anxiety associated with reproductive physiology), and to modify appetite (increasing food intake).<sup>29-35</sup> Ovariectomized bitches and neutered cats fed ad libitum have been shown to significantly gain weight at least in part due to increased food intake.<sup>29-35</sup> Two studies estimated an average doubling of body fat in neutered cats fed ad libitum, with an additional small increase in LBM (10% shown in one study, due to muscle) necessary to support the increased weight.<sup>33,35</sup> An average 31% weight gain over 12 months, largely due to increased body fat, was shown in neutered female colony -housed cats fed ad libitum.<sup>33</sup> Two studies in colony-housed research cats suggest that restricting food intake by approximately 1/3 of amounts recommended for adult maintenance (70 to 90 kcal/kg/day for the adult cat, 50 to 70 kcal/kg/day for inactive adult cats) prevents weight gain in neutered individuals.<sup>31,33</sup> This effect is modified by age at the time of neutering, with less extreme caloric restrictions required in individuals neutered as middle-aged adults. Recent studies by the author estimating RER using indirect calorimetry (age and size matched pairs of intact and neutered dogs) suggests that difference in daily activity level (calculated from dietary history during an interval of stable body weight) rather than RER has a larger influence promoting weight gain in neutered individuals. This is consistent with prior observations in ovariectomized meal-fed (fixed portions) colony-housed bitches where regular exercise thwarted weight gain.<sup>36</sup> Collectively then, various studies substantiate that neutering complexly influences feeding patterns and energy utilization in ways that lead to weight gain. Thus, it is clear that calorie restriction should be recommended soon after neutering, within a few weeks of the procedure in many animals, and that an exercise program should also be encouraged.

## FACTORS INFLUENCING ENERGY UTILIZATION

The common unifying factor in all circumstances of obesity is energy intake exceeding DER with the “extra” fuel being efficiently stored as triglyceride in adipose tissue. Becoming over-conditioned to the point of obesity complexly influences energy utilization. Low activity imposed by excessive weight gain, reduction in the relative proportion of LBM, and altered tissue energy utilization have each been substantiated in a variety of animal species. While having

greater body mass results in larger energy expenditures for physical activity (including respiratory effort), simply being overweight can deter the initiative for voluntary activity. When significant weight loss occurs as a result of an effective weight reduction program, DER changes depending on the respective effects of factors influencing the following three important components of daily total energy expenditure (TEE):

1. Resting Energy Requirement (RER)
2. Thermic Effect of Food (TEF)
3. Exercise Energy Expenditure (EEE; the most variable component of TEE)

During a weight reduction program, RER may decrease if LBM declines as this is where most energy utilization occurs. The TEF represents the energy cost of absorbing, processing and storing nutrients.<sup>37</sup> The thermic effects of nutrients, expressed based on efficiency of energy utilization (subtracting values of thermic effects from a theoretical 100% efficiency) is 70–75% for proteins, 92–94% for carbohydrates, and 97–98% for lipids.<sup>28,37</sup> The TEF is influenced by the number of meals fed per day (higher cost with more numerous meals), amount of food allowed per meal (less food lowers TEF), and the energy sources used in the weight loss formula. Owing to reduced body mass, a given rate of physical activity requires a smaller EEE as weight reduction is realized. Consequently, progressively declining TEE often parallels successful weight loss. This phenomenon may decrease the rate of weight loss over time unless energy allocations are individually titrated to the patient's response, especially during the latter weeks of a weight loss regimen. However, these effects may be offset by increased patient mobility and activity. In some cases this represents an increased "quest for more food" while in others the animal has increased interest in grooming and in interaction with its owner, housemate pets, and the environment and will voluntarily exercise. These behaviors encourage client compliance with the weight loss protocol.

### Factors Favoring Obesity in Cats and Dogs

Many factors favor development of obesity. These include: sedentary living, being neutered, being restricted to indoors, ad libitum feeding of dry food, having liberal access to highly palatable or high-fat foods, the tendency for owners to provide extra food sources (table foods, treats), and importantly, owners failing to feed to response, unintentionally providing too much food by failing to titrate intake to achieve a stable optimal body condition. Surveys suggest that owners commonly provide treats or food additional to the pet's regular meal.<sup>24,38-42</sup> The form of a diet and its nutritional composition also can influence the quantity eaten; for example, certain tastes and canned or semi-moist diets are preferred by some pets.<sup>3,29,38</sup> The highest risks for obesity occur in the young adult to early senior adult years reaching a maximum at 6–9 years, and declining after 12

years.<sup>5</sup> Overall, the lack of adjustment of energy intake to energy expenditure is the critical issue. In man, daily variations in food intake are large (coefficient of variation of  $\pm 23\%$ ) whereas daily variations in energy use are small (approximated as  $\pm 2\%$ ).<sup>28,43,44</sup> Thus, in man, food intake is the most important determinant of altered energy balance.<sup>28</sup> A similar situation also likely exists in pet dogs and cats where "extras" are commonly fed or when ad libitum feeding is permitted.<sup>38-42</sup>

### Obesity-Related Health Risks

Detrimental effects on health and longevity have been shown for obesity in human beings. Associations between specific organ systems, metabolic functions, and conditions thought also to affect dogs and cats are shown in **Table 1**.<sup>2,3,45-48</sup> While the health implications of being overweight and obese have been less studied in dogs and cats as compared to rodents, non-human primates, and human beings, a recently published longitudinal study in kennel-housed Labrador Retrievers demonstrated that leaner body condition reduces the number and onset of chronic diseases and significantly prolonged median lifespan by 2 years; **Figure 5**.<sup>48</sup>

Obesity also can complicate routine veterinary care including physical examination, imaging (radiography and ultrasonography) of body cavities, venipuncture (venous and arterial), cystocentesis, collection of CSF and synovial fluid samples, and may render routine surgical and anesthetic procedures difficult or hazardous. A considerable danger is created by over-estimation of therapeutic fluid and drug dose recommendations, which generally are based on weight at ideal body condition (eg, 15% body composition of fat).

### Defining and Estimating the Extent or Severity of Obesity

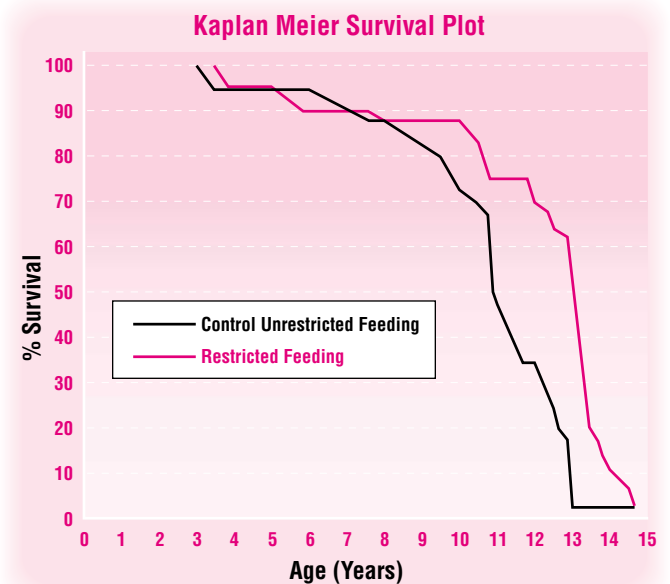
In ideal body condition (ideal body weight [IBW]), approximately 15% of total body weight is comprised of fat. In dogs and cats, this is usually attained at around maturity at 1 year of age. In humans, obesity is defined when body fat exceeds 25–33% of BW.<sup>49</sup> In dogs and cats, most clinicians agree that obesity exists when adiposity causes body mass to exceed IBW by 120%.<sup>47</sup> Considering that at IBW approximately 15% of body weight is fat in the dog, an obese individual with an IBW of 120% would have approximately 35% of body weight attributed to fat. In the obese individual, fat accumulation is thought to cause physiologic impairment. Although the best methods for establishing the degree of adiposity involve objective measures of body fat, these are accomplished using methods that quantitatively estimate body compartments (eg, X-ray absorptiometry, stable isotope [deuterium] or bromide body water dispersal; bioelectrical impedance analysis) that vary widely in expense, accuracy, and complexity, and at present remain impractical for routine use. Consequently, subjective estimates are made based

**Table 1.** Conditions associated with or exacerbated by obesity in man, dogs, and/or cats

Altered Physiologic Functions	Reduced Exercise Tolerance	Organ and Metabolic Alterations
<p><b>Respiratory System</b></p> <ul style="list-style-type: none"> <li>reduced chest wall compliance</li> <li>larger pulmonary blood volume                             <ul style="list-style-type: none"> <li>closure of dependent airways</li> </ul> </li> <li>increased A-a gradient: morbid obesity (man)</li> <li>obesity hypoventilation syndrome: man</li> <li>hyperthermia: impaired heat dissipation</li> </ul> <p><b>Cardiovascular System</b></p> <ul style="list-style-type: none"> <li>increased blood volume</li> <li>increased preload: diastolic filling</li> <li>increased cardiac output</li> <li>hypertension (proven in man, dogs)</li> </ul> <p><b>Pharmacology</b></p> <ul style="list-style-type: none"> <li>drug distribution: water vs fat dispersal</li> <li>inappropriate dosing of fluids and drugs</li> </ul> <p><b>Reproductive</b></p> <ul style="list-style-type: none"> <li>altered hormone metabolism</li> <li>increased risk for dystocia</li> </ul> <p><b>Urinary</b></p> <ul style="list-style-type: none"> <li>increase feline risk: Feline Lower Urinary Tract Disease</li> </ul>	<p><b>Reduced energy utilization</b></p> <p><b>Muscle:</b></p> <ul style="list-style-type: none"> <li>reduced muscle mass</li> <li>altered muscle metabolism</li> <li>reduced muscle strength</li> </ul> <p><b>Heat Intolerance</b></p> <ul style="list-style-type: none"> <li>reduced heat dissipation</li> </ul> <p><b>Neoplasia</b></p> <ul style="list-style-type: none"> <li>mammary tumors (juvenile obesity; dogs)</li> </ul> <p><b>Functional Effects</b></p> <p><b>Joints:</b></p> <ul style="list-style-type: none"> <li>joint stress: increased weight bearing</li> <li>osteodegenerative changes                             <ul style="list-style-type: none"> <li>stifle arthritis</li> <li>cruciate rupture</li> <li>hip dysplasia</li> </ul> </li> </ul> <p><b>Intervertebral disc disease</b></p> <ul style="list-style-type: none"> <li>instability, disc prolapse</li> </ul> <p><b>Respiratory System</b></p> <ul style="list-style-type: none"> <li>increased susceptibility to ambient hyperthermia</li> </ul>	<p><b>Liver</b></p> <ul style="list-style-type: none"> <li>excess triglyceride storage (cats; hepatic lipidosis)</li> </ul> <p><b>Glucose intolerance</b></p> <p><b>Hyperlipidemia</b></p> <p><b>Endocrinopathies</b></p> <ul style="list-style-type: none"> <li>hyperadrenocorticism</li> <li>hypothyroidism</li> <li>hypopituitarism</li> <li>hypothalamic lesions</li> <li>insulinoma</li> <li>diabetes mellitus</li> </ul> <p><b>Dermatitis</b></p> <ul style="list-style-type: none"> <li>perivulvar/perianal inflammation</li> <li>impaired grooming:                             <ul style="list-style-type: none"> <li>matted coat/dermatitis</li> </ul> </li> </ul> <p><b>Mortality</b></p> <ul style="list-style-type: none"> <li>increased risk of death: obese middle aged cats</li> <li>significantly shorter survival: proven in Labrador retrievers</li> </ul>

on calculation of the relative percentage of ideal body weight (% IBW), body condition scores (BCS), or morphometric indexes (the latter more easily applied to cats).

**Obesity Estimation: Relative Percentage of Ideal Body Weight (% IBW).** Simply recording body weight and comparing to breed standards cannot be used as a definitive measure of obesity in dogs due to the wide range of differences in skeletal frame sizes and conformation. Body weight also cannot be used to objectively determine adiposity in cats owing to the broad range in skeletal frame sizes among individuals. Importantly, it also must be remembered that in very small animals (<15 lbs), enteric contents and urine can impart a significant influence on single weight measurements. In practical application, the IBW is estimated from physical examination, recruiting the owner's opinion, consulting medical records where body weight was recorded during the first 2 adult years or other times when the pet maintained optimal body condition, and having a second unbiased person render an opinion. Calculating the % IBW ( $[\text{current weight}/\text{ideal weight}] \times 100$ ) yields 120% for an animal judged to exceed optimal body weight by 20%.

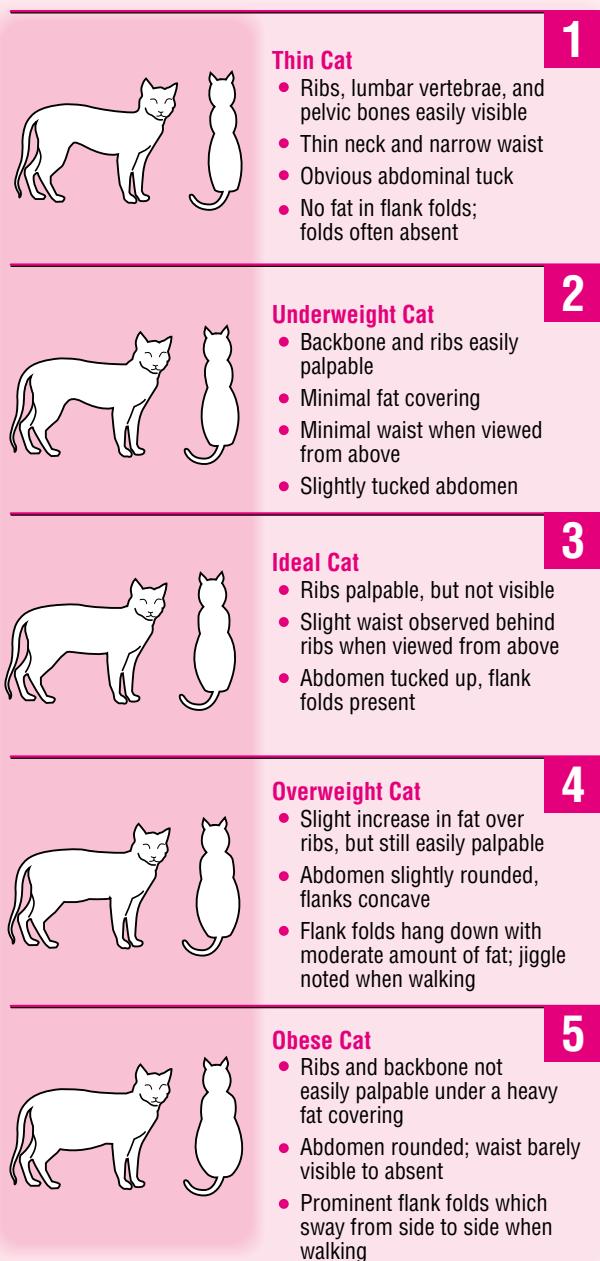


**Figure 5.** Kaplan-Meier survival curve showing the influence of a “slimmer” body composition in pair-fed Labrador Retrievers. Dogs indicated as receiving “restricted feeding” were provided with 75% of the daily energy intake of the control group. A “slimmer” body composition was significantly associated with life span extension. Adapted from reference 48.

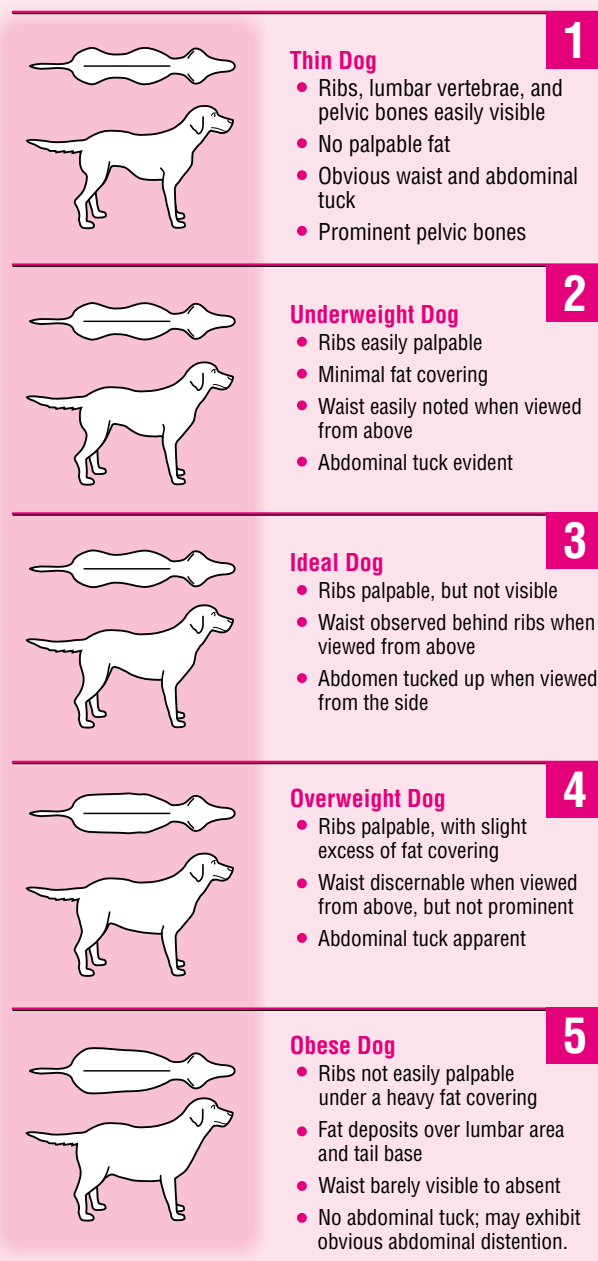
**Obesity Estimation: Body Condition Scoring (BCS).** The BCS provides a subjective assessment of an animal's body fat, taking into account the skeletal frame size and physical assessment of subcutaneous regional and abdominal fat deposition. Systems using either a 5- (with 0.5 increments) or 9-point scale and comparison to physique silhouettes works quite well. This is a learned skill refined with experience and yields the best results when relative assessments are completed by a limited number of examiners.<sup>50,51</sup> Body condition scoring criteria are illustrated in **Figures 6 and 7**.

**Obesity Estimation: Morphometric Measurements.** Estimating total body fat also can be accomplished using

measurements of body regions; in both dogs and cats, the body region that most consistently reflects total body fat is the abdominal (or pelvic) circumference or girth. In addition to abdominal circumference, 1 to 3 other measurements are required to estimate body composition; these account for skeletal frame size or are correlated to LBM. Several measurement schemes have been proposed.<sup>52,53</sup> Such measurements are more difficult to apply to the canine physique; formulae have not been proven for dogs with unique body conformations (brachycephalic or extremely dolichocephalic dogs) or those with body fat >33%.



**Figure 6.** Body condition scoring in cats.



**Figure 7.** Body condition scoring in dogs.

## AN ORGANIZED APPROACH TO WEIGHT REDUCTION

### Client Commitment to Pet Weight Loss

Client recognition of pet obesity and discussion of its detrimental health effects are integral to developing a successful weight loss program. Discussions may be initiated after routine vaccination and health examinations or when current health problems initiate the topic. Display of body condition silhouettes and having the owner identify the silhouette best representing their pet's physique is pivotal in some instances. For others, demonstration of adiposity on a radiograph may convincingly define the problem. The prospect of a more active, healthier pet with fewer health care problems and a longer life are usually persuasive. Cultivating owner participation is encouraged by tangible evidence of weight loss during the first 8 weeks of a weight reduction program using abdominal girth measurements, hospital "weigh ins", and graphic display of the percentage of initial weight lost. Recheck appointments should be quick and convenient to minimize patient and owner stress; a hospital technician can effectively orchestrate these appointments.

Establishing a scheduled "obesity clinic" may encourage client participation by acquainting them with other participants. The most critical component of a successful weight management/reduction program is repetitive evaluation monitoring patient progress and owner compliance with efforts made to renew client enthusiasm, commitment, and patience.

### Baseline Assessments

**Diet History.** It is essential to find out what the overweight animal is currently eating. This is accomplished by acquiring a detailed history of food intake (including brand names, food labels, a complete list of treats with information regarding their caloric density), feeding intervals, and identification of all family members that may participate in providing food sources. Hunting behavior and opportunities for feeding at neighborhood homes or pilfering food from other house pets should also

be ascertained. A questionnaire is used to acquire such information but this is expanded by discussion (**Table 2**). Obtaining a label listing ingredients and energy distribution on an "as fed basis" from the currently fed diet will permit calculation of energy intake. To estimate the caloric density of "extras" fed that are not specifically pet food products, a convenient internet site ([www.nat.uiuc.edu/mainnat.html](http://www.nat.uiuc.edu/mainnat.html)) can be consulted.

**Verify Current Energy Intake.** Owing to the wide range of energy requirements among individuals, determining actual food consumption before entering a weight loss regimen is invaluable. As of 2003, a large number of overweight dogs observed by the author consume less energy than recommended by conventional NRC-based maintenance adult feeding guidelines. A quantitative record of food consumption over a 5-day interval should be collected to allow calculation of

**Table 2.** Client questionnaire used in preparation for a weight reduction protocols

Dietary History	
Date: _____	Animal Name: _____ Case No: _____
Owner Name: _____	Animal Name: _____ Case No: _____
Current food (brand name): _____ (Please provide a package label listing ingredients, protein, fat, and carbohydrate content)	Hospital Fax: _____
Previous types and brands of food used: _____	
Current food fed: Dry or Dry food water moistened or Canned or Semi-moist (packets)	
Quantity/day current food: (cups or tablespoons: EXACT measurement, present your measuring device) _____	
Feeding Frequency: circle one and explain (use back of sheet if necessary) free choice    1 meal    2 meals    > 2 meals    Explain _____	
Extras fed: check box AND quantify amounts — please provide food labels/brands (use back of sheet)	
<input type="checkbox"/> table scraps (specify types — use back if necessary, amount per day) _____	
<input type="checkbox"/> treats: brand name(s) AND size _____ number treats/day _____	
<input type="checkbox"/> food "stolen" from other family pets, specify brand name and quantity/day _____	
<input type="checkbox"/> access to neighborhood food sources? Yes or No If Yes, specify _____	
<input type="checkbox"/> access to prey/demonstrates hunting behavior? Yes or No If Yes: what, when, how much _____	
Number of persons in the family feeding this pet: _____	
Number of other household pets: _____ Specify: _____	
What exercise does your pet regularly participate in? Specify: frequency per day or week, duration, activity, intensity of play/work _____	
Can your pet presently groom distant body regions: back, tail, back of thighs? Yes or No or I don't know	
Have you noted any lamenesses, inability to jump, navigate stairs, or run? Yes or No If Yes, please explain here: _____	
Is your pet currently receiving any medications? Yes or No If Yes, list here exactly what, how much, how frequently, and reason for medication. _____	
Duration of weight problem: _____	
Control measures or weight reduction protocols previously used: describe _____	
What do you estimate to be your pets ideal body weight? (express in pounds; weight at age 1 year may approximate IBW) _____	
<b>Re-evaluation appointments are necessary for supervision of your pet's weight loss.</b>	
What time of day and what day of the week would be most convenient for your schedule? _____	
Feeding daily food allowance is best done in 2 or more meals. How many meal intervals could you accommodate? Circle: 1 2 3 4	
Day Food Intake: Total Energy per Day Average (include all extra foods: clinician to calculate) _____	



baseline energy intake sustaining the overweight body condition. The owner should be instructed to quantify food intake by determining the size of meal allocations with a measuring cup. Both the fed diet and the measuring device should be physically inspected by the clinician orchestrating the weight loss protocol to determine the accuracy of reported amounts and to verify the recorded units. Acquiring a sample of the fed ration and determining the average weight per measured amount will permit the most accurate calculation of “average” food intake. This baseline intake information will serve as the foundation for initial energy allocations for the weight reduction regimen and also will advise maintenance feeding recommendations after successful weight reduction (as it is obvious that this intake is too generous). This method is far superior to calculating MER or DER from commonly cited formulas and feeding a reduced portion of this estimated energy.

**Baseline Health Assessments.** This should include a detailed medical history, including the time frame over which weight gain occurred, as well as the patient’s acceptance and response to previous diet modifications (ie, for dogs and cats: vomiting, diarrhea, constipation; for cats: hematuria or signs of lower urinary tract disease). Any chronically-administered medications should be identified and their influence on food intake or energy utilization considered (ie, glucocorticoids, anticonvulsants). A thorough physical examination and baseline laboratory tests including a CBC, chemistry profile, and urinalysis are advised. Obese dogs should be tested for hypothyroidism. Routine laboratory tests are scrutinized for evidence of asymptomatic health problems, including glucose intolerance (incipient diabetes mellitus, especially in obese cats), markers of hyperadrenocorticism or hypothyroidism (dogs), evidence of infection, and liver or renal abnormalities. It is important to inspect liver enzymes in cats before initiating a weight loss regimen to determine pre-existent hepatic disease. This is important because the discovery of increased liver enzyme activity after initiated weight loss in an obese cat may erroneously suggest iatrogenic hepatic lipidosis. Urinalysis including urine sediment examination will disclose whether hematuria or crystalluria precede diet change.

## REDUCING STRATEGIES

Although there are several general nutritional approaches to weight reduction, those most successful involve specially formulated reducing diets. These foods are variably supplemented with protein, essential fatty acids, vitamins, minerals, and conditionally essential nutrients to ensure adequate nutriture for normal physiology and to maintain LBM. Reducing rations for energy restricted feeding encompass a variety of nutritional approaches including modification in content of fat and fiber as well as food particle processing (entrapped air or moisture content) to increase the sensation of “fullness”. Feeding bulkier foods may

appease owner anxiety about food restrictions as a larger volume of food can be allocated. The rationale for various diet formulations is a complex topic and will not be discussed here. The importance or benefit of fiber in weight management remains arguable. Inclusion of l-carnitine in reducing rations may enhance mobilization of fatty acids between metabolic compartments (cells and organelles), promote oxidation of fatty acids for energy, conserve LBM, and increase urinary excretion of fatty acid carnitine esters.<sup>54-62</sup> Several studies in obese cats undergoing rapid weight loss suggest that supplementation with l-carnitine can attenuate metabolic and hepatic histologic changes associated with development of hepatic lipidosis and enhance recovery from the syndrome.<sup>59-61</sup>

## What Type of Diet ?

Nutritional support should be provided using a specially formulated weight reduction diet. Using a diet specifically formulated for restricted energy delivery provides higher protein, vitamin, and micronutrient intake for maintaining normal metabolism and for preserving LBM during weight loss as compared to the restricted feeding of an adult maintenance ration. The nutritional goal is to have energy deficits met by catabolism of body fat. This objective requires that the rate of weight loss be controlled and that a protein sufficient diet be provided. Since adipose tissue consumes relatively small amounts of energy, maintenance of LBM helps to stabilize energy utilization in the face of reducing total body weight. If weight loss is too rapid, loss of LBM may diminish energy utilization requiring further titrated restriction of energy intake. However, the situation is complicated in that increased activity often is a favorable consequence of weight loss; this will assist in maintaining the rate of weight loss with the original food allowance. The bottom line is that astute observation and individualization of the weight loss regimen is imperative to balance energy intake with apparent need. Attention to the rate of weight loss is essential in this regard, as discussed below.

## What Reducing Diet Should You Recommend?

Owner preference for dry or canned food takes first selection priority. However, final selection of which specially-formulated reducing diet is used should ultimately be the patient’s decision. Several diets that comply with owner preferences (dry, canned, low fiber or fiber supplemented) are sent home where “taste trials” can be conducted. It is important that the obese pet undergoing weight loss eats the newly introduced reducing diet.

## How to Introduce the Weight Loss Diet?

The new diet is transitioned to the patient by introducing an approximate 10 to 15% daily replacement exchange with the current maintenance food. After 6 to 10 days the new reducing ration comprises the patient’s entire food source. Especially in cats, the owner must be cautioned against a

rapid diet transition because of the hazard of self-enforced anorexia and risk of hepatic lipidosis in the obese cat developing the phenomena described as “feline food aversion”.

### How Often to Feed?

Animals on weight reduction programs should be fed multiple small meals per day rather than a single large meal. Feeding of several meals daily may reduce begging behaviors and increase energy used in food assimilation/digestion, sustaining a higher metabolic rate (thermic effect of food, meal-induced thermogenesis).<sup>63</sup> This also may assuage owner anxiety about food restriction. Unfortunately, since many obese animals have a voracious appetite, free choice feeding is typically not an option.

### How Much Energy to Allow?

Many different equations, methods, and feeding recommendations have been advised for determining energy intake to achieve weight loss. The range of energy allocations suggested using various equations or calculation methods is evidence that a single approach cannot be advocated for all individuals. The most reliable method of determining initial caloric intake for a weight loss protocol is to determine the current daily energy intake that has generated and maintained the over-conditioned body weight, as previously described (*see Verify Current Energy Intake*). Comparing the measured daily energy intake with predicted MER or DER for the patient’s IBW may demonstrate the relative “overfeeding” that promoted the over-conditioned status. This exercise demonstrates the lower activity coefficient needed to maintain an IBW for many obese patients.

The activity coefficient is the factor multiplied by the body weight with kilogram (kg) weight expressed at the <sup>0.67</sup> or <sup>0.75</sup> exponent (power). Calculation of RER for IBW has been recommended using several equations:  $99 (BWkg^{0.67})$ ,  $70 (BWkg^{0.75})$ , or  $[30(BWkg) + 70]$  (for animals weighing between 2 and 45 kg). For normally active dogs, DER is proposed to range between 1.4 to 1.8 times RER (eg,  $1.4$  to  $1.8 \times 99[kg]^{0.67}$ ), for normally active adult cats to range between 1.2 to 1.6 times RER, and for obese-prone cats to range between 0.8 to 1.0 times RER.<sup>64</sup> However, many obese pets require greater restrictions than derived using these baseline calculations. While the extremes of DER requirements are diverse owing to a large number of variables, recent studies in pet dogs support that a range of 0.8 to 1.4 times RER more accurately describes DER, with values ranging from  $<99$  to  $106 (IBWkg^{0.67})$  to  $105\text{--}112 (IBWkg^{0.75})$ .<sup>21-24</sup> The importance of individual titration of energy restriction during weight loss in obese animals was recently illustrated in a study involving over-conditioned (average BCS of 4.3) kennel-housed Beagle dogs.<sup>65</sup> Energy titration necessary to achieve a 2% rate of weight loss and target ideal body weight showed that females required a 54% and males a 74% energy restriction from the NRC recommended MER ( $132 \text{ kcal/kg}^{0.75}$ ). Thus energy allocations approximated 71 and 98 kcal/kg<sup>0.75</sup> IBW

per day for the female and male kennel-housed dogs, respectively.

Considering the wide range of values predicted for RER and the subjective nature of IBW estimation in clinical practice, using an averaged 5 day measured energy intake as the baseline for energy restriction provides a margin of confidence and safety for initial feeding recommendations. Once the daily intake has been determined by measurement (based on the owners’ 5 day feeding diary), energy intake is restricted to a level of 60 to 80% for dogs.

For cats, calculation of DER for IBW on the basis of  $1.2 \times \text{RER}$  ( $\text{RER} = 70 (BWkg^{0.75})$  or  $[30(BWkg) + 70]$ ) yields approximately  $84\text{--}98 (BWkg^{0.75})$  or  $60 [IBW(kg)]$  as an estimate. Providing 60% of this amount ( $60 \text{ kcal/kg} \times 0.6$ ) is a reasonable starting energy allocation for obese cats with IBW ranging up to 6 kg. Cats with an IBW ranging between 7 to 9 kg are initially allowed 70% of  $1.2 \times \text{RER}$  or 60 kcal/kg for their IBW and those with IBW ranging between 10–11 kg are initially allowed 80% of  $1.2 \times \text{RER}$  or 60 kcal/kg for their IBW. However, the author has witnessed that a number of morbidly obese cats consume less energy than these formula predictions. Consequently, it also is safer in cats to measure daily food intake for 5 days and to calculate their average daily intake. Cats can then be safely introduced to a weight management program by restricting their daily energy allowance to 80% of the measured baseline intake, rechecking their status in 10 to 14 days, and adjusting restrictions as needed.

In all cases, safe weight loss is maintained by comparing/reconciling energy allocations and actual intake, and carefully monitoring body weight changes during the weight reduction protocol.

### How Much of the Selected Ration?

The quantity of the selected ration to feed is based on its energy density on an “as fed” basis. This calculation should be entered as the quantity of food allowed (to be measured out) on the weight loss protocol log sent home with the client (*Table 3*); a copy of this log also should be placed in the medical record. The owner must be advised that the food allocations will likely be revised depending on their pet’s progress. Recommended meal sizes should be able to be conveniently measured. Using an inexpensive plastic container (such as those used for urine collection) and marking a “fill line” with indelible ink, assists owner adherence to feeding recommendations. For small dogs and cats, the quantity of food to be fed may require determination of “morsel” weight vs volume or “number of kibbles permitted per meal” in order to accurately control food allowances.

It is important that the owner verify food consumption in obese cats, particularly after initial introduction of the “novel” reducing diet. The quantity of food consumed per day should be verified and recorded as this not only detects voluntary fasting but also provides the basis for further adjustments in energy intake.



using a gate, door, hook and eye arrangement on a door to segregate small and large pets, place cat food in an elevated position to limit availability to an obese dog), and finally,

- 5) prohibit opportunities for “grazing” on food spilled from a toddler’s high chair as this also can thwart success of weight loss/management programs.

### What About Exercise?

Increasing exercise (walks, retrieval play/activity, swimming, jogging) and activities interactive with the owner or a companion pet will increase energy utilization. Exactly how much exercise is needed varies markedly among individuals. The goal is to increase energy utilization without increasing energy intake. As much exercise as is reasonably possible and appropriate for the patient’s health status and permitted by the owners lifestyle should be encouraged. Activity for 30 to 60 minutes per day is the minimum amount advised. In addition to direct energy utilization, exercise also conditions muscles maintaining LBM where over 95% of energy utilization occurs. Exercise or play intervals also can distract a “gluttonous” pet’s quest for food. Many cats can be enticed to chase or “combat” objects in interactive play with strings, feathers and other toys, to chase “laser-pointer” light spots, and some also can be taught to accompany their owners on leash walks.

### What to Do When the Obese Pet Fails to Lose Weight ?

**Titration Energy Intake.** Whether or not the initial energy allocation is appropriate will be apparent within the first 4 weeks of a weight reduction protocol. Failure to lose at least 1% of initial body weight per week dictates the need for further energy restriction. However, before energy restriction is increased, it is essential that body weight and condition be verified, owner compliance reviewed, and that pet access to other food sources in the home or neighborhood have been eliminated. If there are no breaches in protocol compliance, caloric intake is further restricted by an additional 10 to 20%; multiply the current energy intake by 90 or 80%, respectively. Subsequent titrations are made using similar downward increments. Whenever energy intake is further restricted, recheck evaluations are mandatory within 2 week intervals. An example of energy titration in a morbidly obese cat with an unusually low RER and activity is shown in **Figure 8**.

### Recheck Appointments — How Often?

Animals undergoing weight reduction should be re-evaluated initially at 2-week intervals until it is clear that an appropriate energy allowance is achieving a safe rate of weight loss. Thereafter, quick re-evaluation appointments occur at 4-week intervals. Interim phone calls to the owner should be made to detect problems and to encourage compliance with the weight loss regimen. Re-evaluations near the predicted closure of a weight loss protocol usually occur

at 2-week intervals as the rate of weight loss may decline requiring further energy restrictions to achieve goal or target weight and body condition.

## CLINICAL MONITORING DURING WEIGHT LOSS

*Baseline body weight and abdominal (pelvic) girth* are measured on week 0, and then at selected intervals. Measurements are made at the *same time of day* and weights should be determined using *calibrated scales* (use a pediatric scale for small dogs and cats). An *indelible ink mark* identifies the site for consistent girth (pelvic) measurements made using a single measuring tape, consistent operator and technique, with length recorded in centimeters. Acquiring *two to three baseline measurements* at different times of day for each parameter verifies that changes are not due to operator technique (girth determination) or retained urinary and enteric contents. Thereafter, *standardization as to the time of day* measurements are made to assist in controlling influences on weight and girth associated with eating and elimination patterns. As previously explained, *frequent body weights during the first six weeks and at the end of the weight loss protocol* (2-week intervals) are important to permit fine-tuning of energy allowances.

**Re-evaluations.** These should include a *quick physical examination and review of the recent diet diary* documenting daily energy intake. Recheck examinations should be brief to minimize client inconvenience and patient stress. Scheduling such visits at the end of a day within a designated time restricted to expedient outpatient services is helpful. A technician can orchestrate these visits.

**Graphically Display Body Weight and Girth Change.** Weight and girth measurements should be graphically displayed to illustrate patient status, encourage the client, and to facilitate adjustment of energy allocations (**Figure 9**). While graphic depiction of the rate of weight loss over 6 to 8 weeks can be used to predict when the weight reduction program will achieve goal weight, such predictions are notoriously unreliable owing the need for frequent adjustment of energy allowances.

**If Signs of Illness Appear.** At any time during the weight reduction protocol, signs of illness *must be investigated* through complete physical examination by a veterinarian familiar with the patient and submission of a CBC, biochemical profile and complete urinalysis. In cats, urine should be tested for bilirubin; bilirubinuria in the cat is always abnormal and alerts the clinician to occult hyperbilirubinemia that may reflect hepatic lipidosis. Cats with hepatic lipidosis typically also develop increased transaminase (ALT, AST) and alkaline phosphatase (ALP) activities, along with bilirubinuria as early syndrome abnormalities.

### Encouraging Your Client

Client participation in monitoring the success of a weight loss protocol encourages their resolve to continue. Demonstration of reducing abdominal girth and weight,

and an improved BCS are strong positive indicators of success. Photographing the patient before weight loss and then sequentially during the weight loss protocol, facilitates owner involvement. Posting “before and after” photos in the record documents success and can provide an encour-

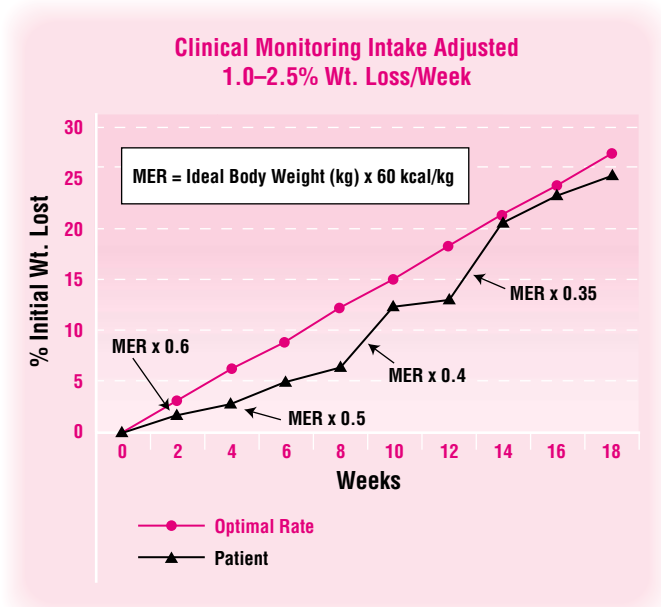
aging display for other clients with obese pets. With digital photography, this can be accomplished rapidly and with minimal cost.

## Weight Control: What Happens After Weight Reduction?

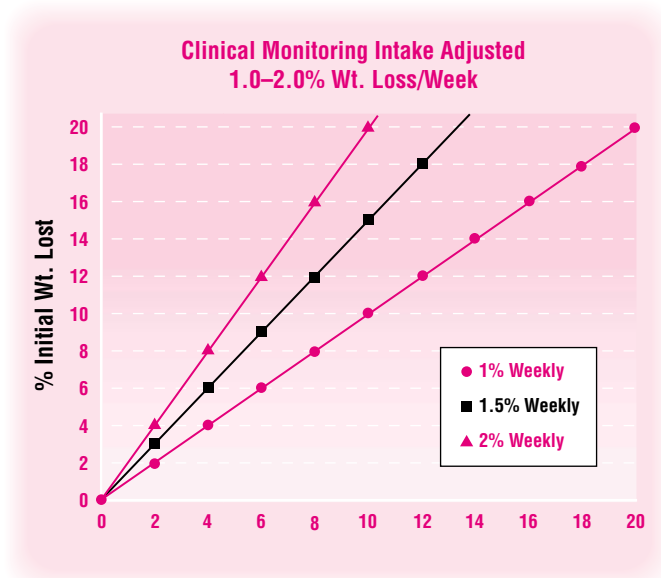
Rebound weight gain occurs in previously obese animals similar to the situation in obese human beings. In man and in dogs, weight rebound is most extreme when weight is lost rapidly.<sup>66</sup> Rebound weight gain may be more prevalent in animals allowed access to a high-fat diet after weight reduction. This phenomenon is shown in **Figure 10** where nearly 50% of weight loss achieved in 32 obese cats over 112 days (average loss was 19% initial body weight) was rapidly regained over a 14-day interval. During this time, cats were permitted ad libitum feeding opportunities of an energy-dense (4.9 kcal/gm) diet. An apparent augmented rate of weight gain after successful weight reduction may reflect a lower total daily energy expenditure at the newly reduced body weight and possibly, a lower rate of fatty acid oxidation. It is during this time that consumption of a fat-restricted diet may be most useful.

## CONCLUSION

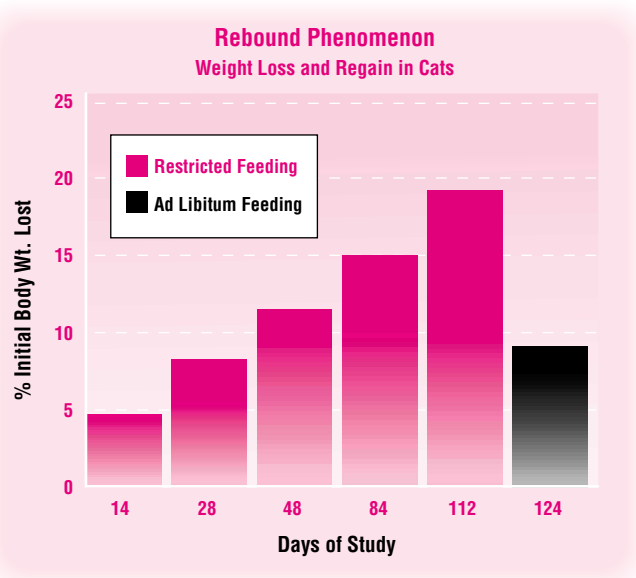
To sustain optimal body weight and condition in a previously obese pet, the owner’s feeding habits and the pet’s eating opportunities must be permanently modified. Encouraging a consistent exercise program also is important. Modification of a sedentary lifestyle may be possible through introduction of toys, climbing stations for cats, interactive play with owners, or acquisition of a companion pet. Long-



**Figure 8.** Graphic representation of individuation of weight loss protocol for an obese cat where energy allowances based on an initial calculation of 60 kcal/kg ideal body weight  $\times$  0.6 was gradually restricted over time to a total 35% energy allowance to achieve desired body weight. Full achievement of ideal body weight required over 40 weeks. An optimal safe rate of weight loss (1.5% of initial body weight per week) is indicated by the dotted line.



**Figure 9.** Sample graphics for recording change in initial body weight during a weight reduction protocol. Rates of weight loss are indicated for comparison purposes ranging between 1.0 and 2.0% of initial weight lost per week.



**Figure 10.** “Rebound phenomenon” as observed in colony-housed obese cats that had gradually lost 18 to 20% of initial body weight over 112 days of energy restriction. Re-introduction of an energy-dense, highly palatable food, provided ad libitum resulted in the regain of 50% of lost body weight over a 12-day interval.

term weight control in previously obese animals can be accomplished with maintenance diets appropriate for the pet's life stage. Owners must follow initial feeding guidelines and adjust energy intake to their pets response to achieve and maintain a stable ideal body weight and condition. Selection of diets with a low caloric density, avoidance of high-fat rations, and continued use of set meal times (avoiding free choice feeding of maintenance dry foods) are each helpful long-term considerations for pets with a history of over-conditioning. One of the most important obstacles to long-term weight management in a gluttonous animal is feeding opportunities derived from meals fed to companion pets. This circumstance may require ingenious methods for achieving physical segregation of the formerly obese pet from feeding stations of its companion housemates.

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