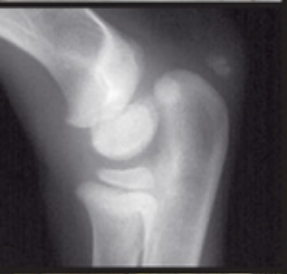
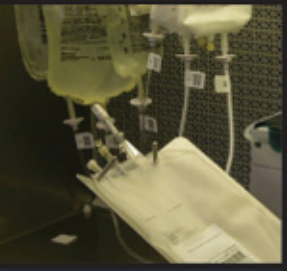
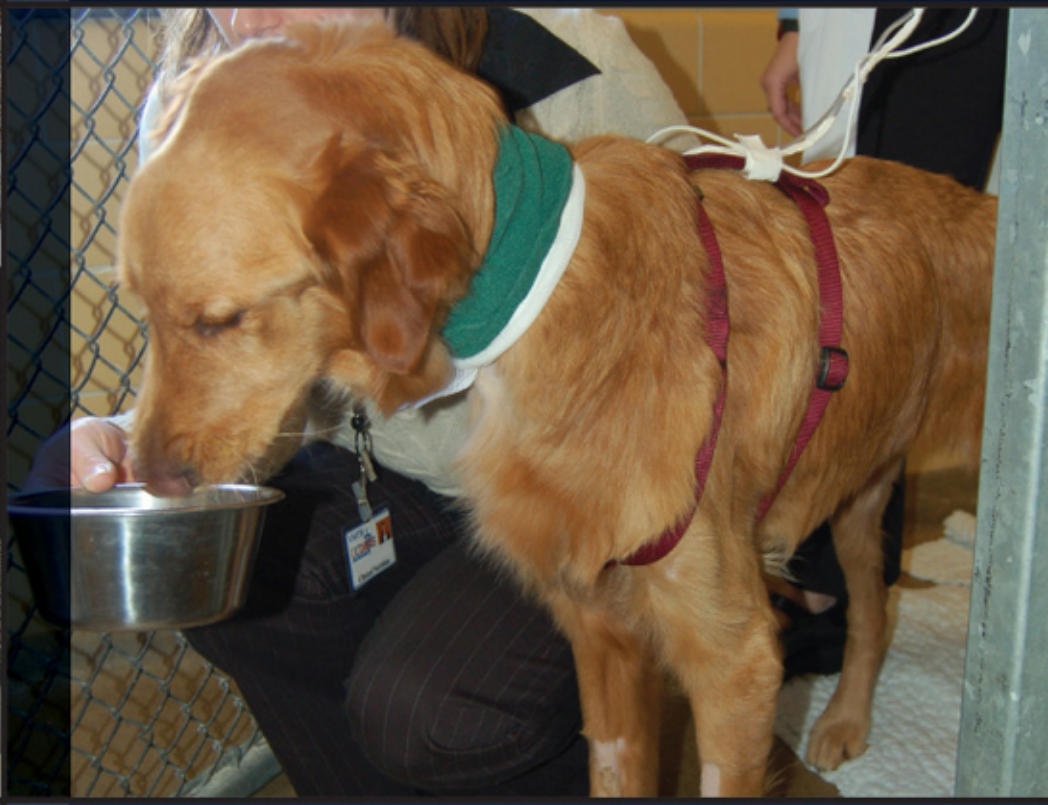
APPLIED VETERINARY CLINICAL NUTRITION

Edited by Andrea J. Fascetti and Sean J. Delaney







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Applied Veterinary Clinical Nutrition

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Preface and Acknowledgments

Nutrition is rarely the first thing the practicing veterinarian considers when making medical recommendations for their patients. Yet eating is one of the only activities every one of our patients does every day, thereby underscoring the importance of the right diet and feeding practices. In fact, appropriate food choices and feeding practices to maintain a lean body condition are the only things in veterinary medicine proven to extend life expectancy in dogs (Kealy et al. 2002). Given that overweight and obese cats are at risk of developing diseases such as diabetes mellitus and hepatic lipidosis that often shorten their life span, one can confidently speculate that this finding may apply to cats as well.

However, as of this writing, only about half of the veterinary schools or colleges in the United States have a board-certified nutritionist as part of their faculty. This means that approximately half of graduating veterinarians never have consistent exposure to practicing nutritionists during their didactic and clinical training so that they can learn how to make appropriate nutritional recommendations to their patients.

The objective of this book is to provide clinically applicable nutritional advice that can be used every day in practice. The foundation and science behind these recommendations is briefly explored, providing the reader with extensive references for further reading if desired. Most of the contributors to this text are nutritionists who are practicing day to day and providing practical solutions for their patients and referring veterinarians.

We envision this text to be a resource not only for the veterinary practitioner but also for students and residents of multiple disciplines. Many veterinary schools and universities are now teaching a course in small animal clinical nutrition, and this text will make a nice complement to such lecture material. The book commences with an exploration of how nutrition can be integrated into everyday practice in a manner that benefits both your patients and your practice. The chapters that follow include a succinct overview of basic nutrition, energy requirements, and the basics of product guides, pet foods, home-prepared diets, and dietary supplements. The basic principles of these foundation chapters are then underscored throughout the remainder of the book, which addresses feeding principles and practices in healthy dogs and cats, as well as those in various disease states. The final two chapters provide guidance for assisted feeding in any patient using enteral and parenteral nutrition.

We are extremely thankful to the editors and staff at Wiley-Blackwell for their constant patience and encouragement with regard to this textbook. We are especially grateful to Nancy Turner, Justin Jeffryes, Erica Judisch, and Carrie Horn of Wiley-Blackwell and copy editor, William Krol, for their efforts in seeing this book to completion.

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None of this would have been possible without the love, support, and guidance from many of our mentors, colleagues, friends, and family throughout the years. Each of us would like to briefly acknowledge them.

Andrea J. Fascetti:
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scientific integrity, and knowledge are characteristics I will strive to emulate throughout my career. It has been a privilege and an honor to work with you both.

I am very thankful to be at a veterinary school where the administration has had the vision to institute and maintain an active clinical and basic research program in nutrition. I am also fortunate to have two amazing colleagues, Dr. Jennifer Larsen and Dr. Jon Ramsey, who share my love of teaching, research, and service in this discipline. Special thanks to Debbie Bee and Dr. Zengshou Yu: Your tremendous efforts in our research facilities make much of what we do possible.

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I think that it is through our relationships with others that we find meaning in life, and no relationships are more important to me than those with my family. My parents, Shirley and Alfred Fascetti, raised me to believe that anything is possible. I am grateful for the sacrifices they made to ensure my success and for their unwavering love and support. I also want to express a heartfelt thanks to my brother, Michael, and sister-in-law, Sara, for their constant support. I am very fortunate to be able to share my passion for learning and research with my husband, Dr. Greg Pasternack. He has been a continual source of encouragement, support, and love throughout this process; and I can't imagine my life without him. To my sons, Noah and Ari, thank you for reminding me every day that it is the little things in life that matter and that we sometimes need to slow down to really appreciate what we have. I also want to say thank you to the many animals that have shared my life and were an inspiration for my career choice: my cats Travis, Beaver, Mario, and Simon, and my dogs, Bandit and Hetchy.

Sean J. Delaney:
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REFERENCE

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Applied Veterinary Clinical Nutrition

Integration of Nutrition into Clinical Practice

1

Sean J. Delaney, Andrea J. Fascetti, and Paul Brentson

INTRODUCTION

A vast majority of veterinarians are forced by necessity to concurrently be businesspeople. This reality, which for many is undesirable, causes many clinical approaches to be at least partially viewed through a "fiscal filter." Although this filter should not be fine enough to strain out appropriate medical decisions, it certainly requires that the economics associated with certain medical practices be considered. Therefore, this introductory chapter will discuss the "business" of nutrition in clinical practice, as to not do so may prevent the reader from being able to afford to implement the knowledge contained in the rest of this textbook.

AVERAGE REVENUE FROM FOOD SALES AND THE POTENTIAL

In 2003, the average food revenue was 4% of total veterinary practice revenue in the United States (Landeck 2006). At the same time, average total revenue earned by practices in 2005 was U.S. $1,078,087. Assuming that the vast majority of food sales were for therapeutic foods that typically have a markup of 40–45%, food sales represent U.S. $43,123, in revenue or gross profits ranging from $17,249 to $19,405. Since net income (before any owner compensation) averaged 25.5% of revenues in 2005, food sales roughly represent between 6.3% and 7.1% of an average practice's gross profits. This value, while relatively significant, can be higher as practices that focus more on the large compliance gap with therapeutic food recommendations (this gap includes both veterinarians who do not actively recommend medically needed foods and clients who do not choose to feed them) can easily double gross profits from food sales with minimal additional effort or expenditures. Theoretically, revenues and profits could be increased more than fivefold based on the low compliance found in a study by the American Animal Hospital Association (AAHA 2003). Thus, many practices could earn up to $100,000 in gross profits from therapeutic pet food sales if they engaged in full compliance.

STRATEGIES TO INCREASE PRODUCT SALES

Recommending an Effective Therapeutic Food

The surest way to increase compliance and therapeutic pet food sales is to recommend an effective one. This sounds simple enough but can be quite challenging in practice. To start, one must make the correct diagnosis and select a food that can be measurably shown to, or perceived to, improve the pet's condition or disease management. For example, clients feeding a "weight loss" food that does not result in weight loss and/or a reduction of or relief in any comorbidity are likely to stop feeding the ineffectual food. Similarly, trying to sell a food that a pet will not eat is unlikely to be successful. Therefore, establishing expectations, monitoring the patient response, and providing a variety of options is vital for client compliance.

Establishing Expectations

Many clients choose not to start feeding a recommended therapeutic food, or choose to stop feeding one, because they do not clearly understand what is expected from the food. Creating expectations requires going over the mechanism by which the food is to prove helpful. For example,

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BOX 1.1

Few recommendations hold as much weight with clients about what to feed their pet as a veterinarian's recommendation. Many pet food companies are aware of this and invest heavily in the veterinary community, vying for the veterinarian's awareness of their products and, ideally, their recommendation. Unfortunately, the resulting influx of generous support is increasingly viewed by some as creating a conflict of interest for veterinarians and resulting in a bias with dietary recommendations. This perception is increased by veterinarians who have limited recommendations beyond the products, brands, and/or companies they stock. Therefore, the goal of this chapter is not to increase the perception among some that veterinarians sell food just to make more money. Instead this chapter's goal is to assist the veterinarian in methods to ensure they can afford to provide the best medical care for their patients and clients by fully integrating nutrition into their clinical practice.

clients who understand that higher dietary phosphorus can cause progression of renal damage in kidney insufficiency, and that most dietary phosphorus comes from protein-rich ingredients, are less likely to feed a higher protein- or phosphorus-containing over-the-counter food. Not surprisingly, clients (in the form of human patients) have better retention of medical information when verbal information is accompanied with written information (Langdon 2002). Therefore, client handouts can be a very useful adjunct to verbal client education. Equally helpful can be reinforcement with repetition of key points by veterinary staff at checkout or discharge, assuming that the staff has already become familiar with all standard client handouts. In some practices, veterinary staff can play an instrumental role in drafting these client handouts as they often can relate to the lay audience and are also aware of the common questions and issues that should be addressed.

Monitoring Patient Response

Although many therapeutic foods can be quite effective, not all foods work for every patient. A food's failure may be defined as simply as a patient being unwilling to eat the food. Therefore, monitoring the response to a newly recommended food is crucial to improving compliance. Initially, the greatest risk to compliance is food refusal. Often this can be managed with appropriate recommendations for transitioning to the new food, as well as planned and periodic follow-up in the form of an email, phone call, or in-person office visit to address any issues that arise. Follow-up is equally important to reinforce the importance of the dietary recommendation. Recommendations that have no follow-up are likely to be perceived as not being as crucial or important. Finally, checking on progress provides an opportunity to discuss and select an alternative but still appropriate food if the first recommendation does not work. At times there can be a reluctance to perform follow-up since it often is "unbillable" time; however, follow-up can be tiered and veterinary support staff can be leveraged to assist with follow-up. Many of the outbound calls can be conducted by reception staff with elevation to licensed veterinary technicians and the attending veterinarian as needed. This "triaging" of sorts can increase efficiency, and often is welcomed by staff members who feel both entrusted and empowered.

Providing a Variety of Options

Since no food will work in every situation, it is important to have additional options for the client. A ready and specific alternative recommendation should reduce the likelihood that the client may select a food by themselves, resulting in the potential for an inappropriate food to be selected and the potential loss of a medically justified sale. The tendency to stock only one "house brand"—while convenient from an inventory management perspective—decreases the ability to readily offer alternatives and can lead to a perception that there is only one option, or worse yet, that the recommendation is made solely on the basis that that particular brand is all the veterinarian sells. Certainly, carrying every therapeutic food available (which now number in the hundreds) is not feasible in all but a few referral settings; therefore, a selection of foods used for the management of diseases seen frequently at the practice along with a willingness to special order, or even identify direct delivery options for clients, is probably the best approach. Additionally, the stocking of more smaller-sized bags can help increase the variety of foods offered without substantially increasing the "carrying cost of inventory." Small bags also can be useful for a trial, and once an acceptable option has been found a standing order for that patient in larger sizes can be created. Such standing orders then help to increase the number of inventory turns, thereby improving cash management. This "small bag" approach might also assist with reducing the labor involved in stocking larger bags as well as increasing the storage capacity of a facility by increasing the height at which food can be stored. Most therapeutic food manufacturers will accept return of inventory that has expired. For

those manufacturers where such is not the case, this approach can minimize "perishable shrink" by reducing the cost of any expired bag that cannot be returned.

From the veterinary practitioner's viewpoint, the greatest value of carrying and recommending a variety of products for the same condition can be increasing one's familiarity with different products. Clinical experience with each product increases the likelihood of making the best initial recommendation, as well as increasing one's comfort with changing to an alternative product if the initial recommendation proves unsuccessful.

Recommending Therapeutic Treats

A growing category within veterinary product offerings is therapeutic treats. These treats often pair with a "matching" therapeutic food to give the client a nutritionally appropriate option when treating is desired. These treats often take the form of a biscuit-shaped version of the corresponding dry kibble. Therefore, treats generally do not offer anything novel to the nutritional management of the condition or disease, but rather assist with compliance by encouraging the pet's interest in the new dietary approach while preventing some other treat, which might be inappropriate, from being given. The same process outlined above should be used when recommending an effective therapeutic food.

Recommending Nutraceuticals and Dietary Supplements

For a full discussion on this subject please see Chapter 5 on nutraceuticals and dietary supplements.

From a financial perspective, stocking certain dietary supplements should be considered. Although the margin on such products can vary greatly, they generally take up much less shelf space than food and treats. Typically, products that are only sold through veterinarians should be considered unless carrying nonexclusive products adds overall "value" for the client due to convenience. Caution should be taken when recommending or offering products for sale at a premium when comparable human supplements of equal or even greater quality or potency are available for a similar or lower price. If such products are available from other retailers, whether "brick and mortar" or online, it is in the best interest of solid client relations to refer clients to that retailer, while being sure to give a specific product and retailer recommendation for clarity and convenience. If a product is widely available only online, then clients are generally willing to purchase such products directly from the veterinarian who can compete on the basis of reduced delivery time and cost.

CREATING OR INCREASING REVENUE FROM NUTRITIONAL ADVICE

Veterinarians' time is limited for both their own continuing education and client education. Therefore, there is an "opportunity cost" associated with spending time on nutrition. If a veterinarian earns more income from learning about and performing surgery, for example, than learning about and advising on nutrition, there is a financial incentive to focus on surgery and a disincentive to focus on nutrition. Certainly the generalist cannot pick and choose only the aspects of veterinary medicine that are most profitable but recognizing the potential for fiscal disparity provides context for a discussion on nutritional advice revenue.

Not only is veterinarians' time limited, the value of nutritional advice can be diluted by the perception that they lack the expertise to make nutritional recommendations. This perception can be increased by the appearance of bias for a particular brand or company's food in one's recommendation(s) as discussed above or by a variety of compounding factors. One of these factors is the belief that nutrition is a pseudoscience. This belief can largely be dispelled by ensuring that the application of nutrition is testable. If a veterinarian forgoes "testing" a nutritional recommendation by neglecting to monitor patient response, then one can hardly blame clients for feeling that their own beliefs about feeding are equally correct. This can be especially true when inappropriate feeding regimens may not manifest as problems immediately. Unfortunately, clients are not aware that veterinarians who recommend a particular therapeutic food often choose to do so because such recommendations are based on scientifically proven strategies or have, in fact, actually been tested for the condition or disease in question. Certainly many therapeutic veterinary foods are in need of additional clinical study (Roudebush et al. 2004); however, they are largely based on very sound science. Clients may also believe that nutrition is simple, after all, as they likely have successfully fed themselves for most of their lives. While providing adequate calories to meet (and often exceed) caloric requirements is thankfully relatively simple in the developed world, ensuring that the nutrients delivered with these calories are optimal is not always straightforward. The field of nutrition is also beset by self-proclaimed "nutritionists" who have little, if any, medical or nutritional training. At the same time, many veterinarians received an abridged veterinary nutrition education in veterinary school or college, and subsequently little additional education postgraduation. This has led to a level of discomfort for many on the subject, rather than the expertise or mastery many feel on

other veterinary medical topics. Thus, a climate exists where veterinarians acquiesce in the nutritional management of their patient, or at least fail to take a very active role unless intervention is absolutely necessary, such as in the cases of hepatic lipidosis or food allergy. Therefore, the following recommendations are for practitioners who take, or wish to take, an active role in the management of all their patients' diets.

Nutritional Advice for Healthy Patients

The number one obligation of the veterinarian when advising clients about an appropriate diet for a healthy pet is to ensure that it maintains an ideal body condition (please see Chapter 9 on the nutritional management of body weight for further discussion on this topic). Keeping dogs lean is the only proven intervention to increase both the quantity and quality of life (Kealy 2002). Although unproven in cats, caloric restriction has repeatedly been shown to extend lifespan in mammals (Sohal 1996; Barja 2004) and would thus be expected to do so in cats as well. Therefore, avoidance of overweight and obesity should be a goal for the feeding of every patient a practitioner sees.

In addition to weight management, an appropriate food should have an appropriate nutritional adequacy statement for the patient. This means that the food is appropriate for the patient's species, age, and reproductive status if the patient is a reproducing female. As would be expected, many foods meet these criteria, and further discrimination should be based on both client and patient preference. For a client, convenience, cost, and personal nutritional philosophy may be important in deciding which foods they select. For patients, ingredients and their associated impact on palatability along with texture (i.e., dry, wet, semi-moist) and macronutrient distribution (e.g., protein, fat, and carbohydrate percentages) play key roles in the foods they choose to consume when given a choice. Recognizing that no one food can meet all of these preferences and needs helps to give a perspective on why so many brands and varieties exist and what needs to be considered when advising clients about food options.

It can often be useful to have the client select a few foods they like and review these products with them during wellness visits. This method helps to narrow down the field of foods to consider and often provides an opportune time to exhibit some expertise, as well as an openness to discuss nutrition. If the client has no preconceived notions, then it should be suggested that companies be recommended that actually make their own food and employ nutritionists. Such companies are more likely to have the technical expertise to address any issues that might arise, as well as the knowledge to make nutritionally sound and safe products.

From a fiscal perspective, such a review of potential foods or nutritional recommendations should not result in a unique charge for the client but rather should be captured in the office visit fee. This assumes that any requested review does not require additional research and analysis outside the office visit. In cases where it does, time should be charged either on an agreed upon flat rate or on a per-unit of time basis up to some pre-established maximum. Clients who do not wish to pay for the veterinarian's time should be advised that the evaluation is accordingly limited. Some veterinarians find it difficult to charge for researching an issue but if the research is specific for a patient, most clients will accept that it is appropriate when it is raised with confidence and the resolve that one's professional time is of value. It should be noted that a veterinarian's review often involves dietary supplements, as the variety of novel and often unconventional supplements greatly exceeds the number of pet foods, which are, in practice, more closely regulated.

At times, veterinarians have difficulty distinguishing the continuing self-study required as a veterinary medicine professional and the work involved in researching unique supplements or foods. The best way to distinguish this in one's own mind is that the veterinarian is not charging for the knowledge on how to interpret and find information, but rather the act of applying their critical thinking and scientific knowledge to the patient's and/or client's specific products and/or needs. An analogy might be that one does not charge for the time it takes to learn a surgical procedure but rather charges for using the resulting skills and knowledge to perform the surgery on particular patients.

Nutritional Advice for Unhealthy Patients

Most, if not all, diseases and conditions can be affected by diet. For some conditions and diseases this may simply be related to the adverse effects of inadequate caloric intake associated with hyporexia or anorexia of illness. For many other conditions and diseases, there are specific nutritional management interventions that are the subject for most of the rest of this textbook. For these sick patients, it is generally easier to generate revenue through veterinary therapeutic foods, treats, and/or parenteral solution sales, or through procedures (such as feeding tube placement) to provide compensation for the specific nutritional guidance and/or advice involved in their selection. However, it should be noted that for board-certified veterinary nutritionists who consult on cases, but who may not share in

or receive credit for such sales or procedures, one should expect to compensate them specifically for their time for such advice. The veterinarian should be able to realize adequate revenue through product sales, nutrition-related procedures, and nutritional counseling to justify the full integration of nutrition into clinical practice to the benefit of healthy and unhealthy patients.

BOX 1.2 WHAT IS A BOARD-CERTIFIED VETERINARY NUTRITIONIST?

A board-certified veterinary nutritionist is a licensed veterinarian who has undergone additional education and training in the field of veterinary nutrition. This typically involves additional graduate coursework and/or graduate degrees in nutrition along with residency training at the secondary or tertiary referral level under the supervision of a board-certified veterinary nutritionist. Following completion of residency training and publication of animal nutrition related research in peer-reviewed scientific journals, candidates for certification often submit case reports along with their credentials to indicate their mastery of the discipline. Upon acceptance of these materials, candidates are allowed to sit for a multipart multiday intensive examination on veterinary nutrition. Candidates who pass all parts of the examination and are voted into the specialty can refer to themselves as board-certified veterinary nutritionists or "diplomates." There are currently two veterinary nutrition specialty colleges in the world, the American College of Veterinary Nutrition (ACVN™; www.acvn.org; also the basis for most of the summary above) and the European College of Veterinary Comparative Nutrition (ECVCN). Members of the ACVN can be found in North America, the Carribean, the United Kingdom, Europe, and Australasia, while most ECVCN diplomates are found in Europe. The majority of diplomates are employed in academia, with the remainder in industry, private practice, or the government. Attending veterinarians and specialists in other disciplines typically refer cases to diplomates of the ACVN or ECVCN in academia or at large referral hospitals.

It is expected that the reader of the rest of this textbook should be able to better advise clients about the nutritional management of unhealthy patients and recognize when referral to a board-certified veterinary nutritionist is indicated. It is recommended that when a board-certified veterinary nutritionist needs to be consulted, the referring veterinarian charges for their time specifically if they act as the "conduit" for the consultation, similar to how clinical pathology reports may be handled. Accordingly, many veterinary nutritionists and veterinary nutrition consulting services will bill the referring veterinarian directly rather than the client so that the referring veterinarian can apply the necessary charges for their time to the client's final invoice. Occasionally, product sales and consulting fees will not be available as methods to compensate the generalist or referring veterinarian. In those cases, a veterinarian should charge for their time or set up an office visit specifically to address an unhealthy patient's nutritional needs and educate the client accordingly.

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Basic Nutrition Overview

2

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INTRODUCTION

While the vast majority of this text is focused on the application of veterinary nutrition in clinical practice, this chapter centers around basic nutrition. Although the chapter is not exhaustive, it should provide enough depth to enable the applied veterinary clinical nutrition portion of the text to be used with a strong understanding of key underlying nutrition principles.

ENERGY

After oxygen and water, the next most important component for any animal to gain from its environment is energy. Energy is available from only three types of macronutrients: protein, fat, and carbohydrate. Each of these macronutrients provides a specific amount of energy that can be measured in kilocalories or kiloJoules or Calories. The amount of energy is determined by knowing the mass of the macronutrient in a food or diet and the corresponding energy conversion factor. Energy conversion factors are standardized values for the amount of energy available from a gram of the specified macronutrient. Currently the most commonly used unit for measuring energy is the pre-International System (SI) metric unit, kilocalories (kcal), which is equal to "Calories" (with an uppercase "C") seen on human food labels in certain countries like the United States (1,000 kcal is often written as "Mcal," the abbreviation for Megacalorie). The less commonly used SI unit for energy, kiloJoule (kJ), is converted from kilocalorie or Calorie by multiplying by 4.185 (1 kcal or Calorie = 4.185 kJ). For pet foods, the energy conversion factors that are used are referred to as modified Atwater factors. They are 3.5 kcal/gram (g) for protein, 8.5 kcal/g for fat, and 3.5 kcal/g for carbohydrate. These values are slightly lower than those used for human foods (i.e., 4 kcal/g for protein, 9 kcal/g for fat, and 4 kcal/g for carbohydrate) due to the typically lower digestibility of ingredients commonly used in pet food (assumed average apparent digestibility for protein is 80%, 90% for fat, and 84% for carbohydrate).

All three macronutrients' energy must ultimately be used to create adenosine triphosphate (ATP) through phosphorylation as ATP is the "energy currency" of the body. For protein this means conversion to glucose via gluconeogenesis with ATP generation via glycolysis and the Krebs or tricarboxylic acid (TCA) cycle during cellular respiration. Gluconeogenesis is the metabolic pathway by which glucogenic amino acids (lysine and leucine excluded) are converted to glucose. Glucose is then converted to pyruvate during glycolysis, which produces ATP and the potential for more ATP if pyruvate enters the TCA cycle. For fat, ATP is typically produced via beta oxidation where ATP is produced from acetyl-CoA in the TCA cycle. Generated glucose or glucose from the breakdown of glycogen or starch and from sugars in the diet can be used to generate ATP via glycolysis and the TCA cycle as well. It should be noted that the TCA cycle produces substantially more ATP than glycolysis that solely generates pyruvate, but the TCA cycle cannot occur in the absence of oxygen, and thus the importance of breathing and the intake of oxygen in the production of energy by the body. However, lactic acid produced during anaerobic glycolysis (typically in muscle) can be converted to glucose by the liver in the Cori cycle.

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It is also worth noting that any protein consumed in excess of needs for anabolic pathways such as protein synthesis will be used as a source of energy as there is no body store for amino acids. This is different from excessive fat, which will be stored in adipose tissue, and glucose, which can be stored as glycogen. All protein, fat, and carbohydrate that exceed energy needs can end up being stored in adipose tissue. Unlike glycogen, theoretically there is no limit in the amount of energy that can be stored in adipose tissue, although there may be adverse health consequences with extreme levels of storage as seen with obesity.

Energy Requirements

Dogs and cats eat to meet their energy needs. Unlike some species that have "specific hungers" for certain nutrients (e.g., ruminants for certain minerals), dogs and cats will not seek out certain foods or nutrients in the face of specific nutrient deficiencies. This makes sense teleologically for a carnivore like the cat or a species that has some carnivorous roots or tendencies like the dog. From an evolutionary perspective, there was (or is) no penalty for the inability to seek out specific nutrients, as the search for and consumption of specific evolutionary prey species should inherently provide the right balance and types of essential nutrients. The only risk for deficiency is really related to inadequate consumption of prey. Therefore, determining a dog's or cat's energy requirement is very important.

Pet foods are generally formulated with a certain amount of nutrient per unit of energy. This ensures that essential nutrients are provided to the dog or cat at appropriate levels when fed to meet the pet's energy requirement. Consequently, this means that pets that are fed such foods below their energy requirement are in danger of nutritional deficiencies. Pets fed above their energy requirement are in danger of receiving excessive amounts of nutrients (this latter case really only represents a risk of obesity or potentially urolithiasis). For further discussion on determining a dog's or cat's energy requirement as well as different energy terms such as gross energy, digestible energy, metabolizable energy, and net energy, the reader is referred to Chapter 3 on energy requirements.

ESSENTIAL NUTRIENTS

Essential nutrients are organic compounds and nonorganic elements that cannot be produced by the body but are needed to support life. Essentiality is different for different species, although for mammalian species such as the dog and the cat, there are many similarities in what is essential; differences are mainly in the amount needed. In addition, there are nutrients that are required only at certain times or under the right circumstances. These nutrients are referred to as "conditionally essential nutrients." An example of a conditionally essential nutrient that also exemplifies interspecies differences in essentiality is the amino acid taurine. In premature human infants, taurine, which is essential for cats but not dogs, is conditionally essential. Premature neonates are not metabolically mature enough to produce adequate amounts of taurine from the normal sulfur amino acid precursors, methionine and cystine.

Cystine is a good example of another category of nutrients that are called "sparing." Sparing nutrients are able to decrease the amount of essential nutrient needed in the diet. Thus, cystine decreases by up to 50% the amount of methionine needed in the diets of both dogs and cats. Cystine is not considered essential as it is not needed in the diet when adequate methionine is present. Methionine itself is sparing for choline as it can also serve as a source of methyl groups. Therefore, methionine is both an essential and a sparing nutrient. The other commonly encountered sparing nutrient is tyrosine, which spares the amino acid phenylalanine and has been shown to be important in maximal melanin synthesis in black cats (Yu 2001).

List of Essential Nutrients for Dogs and Cats by Group

1. Protein
   a. Amino Acids
      i. Arginine
      ii. Histidine
      iii. Isoleucine
      iv. Leucine
      v. Lysine
      vi. Methionine (spared by cystine)
      vii. Phenylalanine (spared by tyrosine)
      viii. Threonine
      ix. Tryptophan
      x. Valine
      xi. Taurine (cat, not dog)
2. Fat
   a. Linoleic acid
   b. Arachidonic acid (cat, not dog)
   c. +/– Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
3. Minerals
   a. Macrominerals (required at ≥100 mg/Mcal, or approx. ≥400 ppm)
      i. Calcium (Ca)

   ii. Phosphorus (P)
   iii. Magnesium (Mg)
   iv. Sodium (Na)
   v. Potassium (K)
   vi. Chloride (Cl)
  b. Trace minerals or microminerals (required at < 100 mg/Mcal, or approx. < 400 ppm)
   i. Iron (Fe)
   ii. Copper (Cu)
   iii. Zinc (Zn)
   iv. Manganese (Mn)
   v. Selenium (Se)
   vi. Iodine (I)
4. Vitamins
  a. Fat-soluble vitamins
   i. Vitamin A, retinol
   ii. Vitamin D3, cholecalciferol
   iii. Vitamin E, α-tocopherol
   iv. +/– Vitamin K3, menadione (also vitamin K1, phylloquinone) (cat, not dog)
  b. Water-soluble vitamins
   i. Thiamin, vitamin B1
   ii. Riboflavin, vitamin B2
   iii. Pyridoxine, vitamin B6
   iv. Niacin, vitamin B3
   v. Pantothenic acid, vitamin B5
   vi. Cobalamin, vitamin B12
   vii. Folic Acid, vitamin B9
   viii. Biotin, vitamin H or B7
   ix. Choline

As cited in the list above, the cat as a true carnivore requires nutrients that the dog as an omnivore does not. The following is a list of the cat's unique metabolics:

- Unable to convert carotenoids to adequate vitamin A/retinol
- Inadequate synthesis of vitamin D (even if hairless and exposed to sunlight/UV radiation)
- Unable to use tryptophan for niacin synthesis
- Unable to synthesize adequate amount of taurine from sulfur amino acids, methionine, and cysteine
- Unable to synthesize citrulline (needed for the urea cycle; as a result, a single arginine-free but protein-containing meal can cause death)
- Glutamic acid (high in plants and low in animals) intolerance
- Reduced ability to conserve nitrogen
- Reduced ability to desaturate long-chain PUFAs (therefore, needs arachidonic acid since cats are unable to make it from linoleic acid)
- Metabolically adapted to low carbohydrate diet (e.g., less activity of enzymes involved in glucose metabolism like glucokinase, which is the enzyme needed for the first step in deriving ATP from glucose)

Protein and Amino Acids

Protein provides nitrogen and amino acids in the diet. Amino acids are either essential or nonessential (aka dispensable). Essential amino acids for dogs and cats include arginine, which is not essential for humans; therefore, arginine or a protein rich in it (e.g., whey) may be added to human enteral diets when fed to dogs or cats. In addition cats require taurine (as noted above), unlike dogs and humans who can make adequate amounts from sulfur amino acid precursors. In commercial pet foods, taurine, like several other commonly limiting amino acids, is supplied as a purified amino acid. Essential amino acids (except taurine) can potentially come in two isoforms: L-amino acids and D-amino acids. L-amino acids are the commonly encountered form, while D-amino acids are less common and at times less available or unavailable for use by the body. For example, D-lysine cannot be used by dogs and cats the way L-lysine can be. However, D-methionine can be used to meet up to 50% of the methionine requirement. Therefore, one should not see a dog or cat food supplemented with D-lysine but can see one supplemented with DL-methionine.

Methionine, in addition to enabling urine acidification, is also used in pet foods that derive a large portion of their protein content from legumes such as soy, which are "limiting" in sulfur amino acids. Limiting means that the particular essential amino acid is closest to the requirement of the species. Therefore, when the species' requirement for that essential amino acid is met, all other essential amino acids the protein provides are in excess of the requirement. Thus, it can be more cost effective for a pet food manufacturer to add a single limiting amino acid in its purified form (likely to be a DL-amino acid) than to simply increase the amount of protein-rich ingredients to meet a single amino acid requirement. In addition to sulfur amino acids that are limiting in legumes, lysine is typically limiting in grains. Ancestral peoples recognized this in a limited way and combined legumes and grains (e.g., "rice and beans") in meals to ensure a complete and balanced amino acid profile.

There are several ways to assess an ingredient's or a food's protein content. The typically required and reported crude protein value does not give any indication of how well a food will meet a dog's or cat's protein or amino acid requirements, although higher crude protein values are

often perceived as better. In fact, crude protein doesn't even represent protein content directly but rather nitrogen content. Then, a standard equation of the nitrogen percentage in the food times 6.25 is used to calculate crude protein. This fact was at the root of the major pet food recall of 2007 where wheat flour was apparently being "spiked" with a cheap nitrogen-rich ingredient—melamine—that formed crystals within the kidney when in the presence of a related chemical—cyanuric acid—resulting in renal failure. Therefore, crude protein is really an indirect measurement of protein quantity and does not provide any information about protein quality. Ideally, a measure of protein quality should provide some insight as to how well a particular source of protein meets the protein and amino acid requirements of a particular species. In general, the higher the quality, the more available essential amino acids the protein source provides. Values for protein quality include:

- Protein efficiency ratio (PER) is the gain in body mass or weight for a subject fed a particular food divided by the mass of the protein intake; higher values mean the protein quality is higher.
- Biological value (BV) is the mass of nitrogen incorporated into the subject's body divided by the mass of nitrogen from protein in the food times 100. A value of 100% (sometimes given to fresh chicken egg protein by convention) means all of the dietary protein eaten and absorbed becomes protein in the body; thus 100% is the absolute maximum with lower values indicating lower quality.
- Net protein utilization (NPU) is the ratio of amino acids converted to protein to the amino acids provided by the food; a value of 1 is the highest value possible and is given to fresh chicken eggs.
- Protein digestibility corrected amino acid score (PDCAAS) is milligrams of limiting amino acid (for humans) in 1 gram of test protein per milligram of the same amino acid in 1 gram of reference protein times true digestibility percentage (fecal); values up to 1 can be achieved, and the closer to 1 the higher the protein quality.

All of the above methods have flaws but generally predict how well a particular protein-rich food will meet an animal's or human's protein and/or amino acid needs. Unfortunately, these values are not reported for pet foods or many protein-rich ingredients used in pet foods.

Fat

Fats play a role in enabling fat-soluble vitamin absorption and provide essential and important fatty acids that serve as precursors for the inflammatory mediators called eicosanoids and become incorporated into cell membranes. The essential fatty acid linoleic acid (LA) is required by both the dog and cat and is 18 carbons long with two double bonds, with the "first" double bond at the sixth carbon from the "omega" end. This means that LA is an n-6 or omega-6 fatty acid (due to the location of the first double bond) that can be referred to as "18:2(n-6)" where the "18" is the carbon chain length and the "2" is for the number of double bonds. Similarly, arachidonic acid [AA; sometimes abbreviated ARA (especially on human infant formula and to distinguish from an abbreviation for amino acid)] can be referred to as "20:4(n-6)" since it has more carbon (20) and double bonds (4). Good sources of LA are vegetable oils or fats from animals raised predominantly on plants rich in LA such as corn-fed chickens. Good sources of AA or ARA are animal fats although gamma-linolenic acid [GLA or 18:3(n-6)] (note the second "n" in linolenic that is not present in linoleic acid or LA) from borage oil and evening primrose oil can be used as a precursor in cats that cannot derive AA or ARA from LA as can humans and dogs. The n-3 or omega-3 fatty acids are thus named because their "first" double bond is at the third carbon from the "omega" end. Terrestrial plants such as flaxseed (aka linseed) can be rich sources of n-3 fatty acids in the form of alpha-linolenic acid [ALA or 18:3(n-3)], but its shorter carbon chain cannot be efficiently elongated to the more "beneficial" long-chain n-3 fatty acids, EPA and DHA. Therefore, marine oils such as algal oil, krill oil, and fish oil are preferred as sources of n-3 fatty acids. Generally, species closest on the food chain to phytoplankton (which can efficiently synthesize the long-chain n-3 fatty acids) are selected to avoid the concurrent issue of bioaccumulation of pollutants. It is worth noting that there is debate about the importance of the ratio of n-6 to long-chain n-3 fatty acids versus the total dietary amount of long-chain n-3 fatty acids (NRC 2006). It would seem that the increased production of the less inflammatory eicosanoids from long-chain n-3 fatty acids would be greatest when the least amount of alternative n-6 fatty acid precursors are available.

Carbohydrates

Although carbohydrates are not essential, they are included here as they provide energy, which is. In addition, carbohydrate-rich ingredients or foods are also the source of dietary fiber, which can be important for normal GI function and health. The measure of fiber is typically reported on pet food labels as crude fiber. This analytical method does not capture all forms of fiber and largely reports the insoluble portion. A better value used for

human foods is total dietary fiber, which includes both soluble and insoluble fibers. Soluble fiber has the ability to "hold" water and generally makes feces softer. Common sources of soluble fiber are fruits and gums, with gums more commonly used in pet food as they are frequently used to improve canned food texture. Insoluble fiber generally increases fecal bulk but does not soften feces as it does not have the ability to absorb water. Insoluble fiber generally comes from grains in the diet (although fiber from whole grains is typically "mixed" with both soluble and insoluble fibers) and is added in the form of cellulose. Many fiber types used for supplementation are "mixed" fibers with mostly soluble fiber characteristics. The best example of a mixed fiber type is psyllium fiber found in products like Metamucil® (Procter & Gamble, Cincinnati, OH). It is also worth noting that many soluble fibers are also fermentable. Fermentable fibers can be used by normal gut bacteria as an energy source and in the process produce short-chain fatty acids that can be used by enterocytes as an energy source. These fermentable fibers are sometimes referred to as prebiotics (for more discussion about fiber and microflora, please see Chapter 12). Also, fiber is often used in the management of diabetes mellitus to reduce postprandial hyperglycemia and weight management to decrease energy density (i.e., kcal per can or cup).

Minerals

Macrominerals

Minerals that are needed by dogs and cats in 100 mg/Mcal or more amounts are generally considered macrominerals. These minerals (e.g., calcium, phosphorus, magnesium, sodium, potassium, and chloride) are commonly provided in intravenous fluids. Typical dietary sources for calcium are bone or calcium salts. Phosphorus comes from protein-rich foods, plants, and bones, and is often supplied in adequate levels in pet foods that use "meals," which can have a significant amount of bone and thus phosphorus. Magnesium, sodium, potassium, and chloride can often be found in the form of salts in pet food. At times, the form of the salt is suggested as important because certain forms are more bioavailable than others. Although this can be the case either due to a truly higher bioavailability or due to a higher potency (i.e., more elemental mineral per unit of mass of salt due to molecular formula differences), most of these differences can be overcome by simply providing more of the salt so that an equivalent amount of the essential element is delivered. However, it should be noted that some mineral salts are poorly available such as oxides, and therefore care should be taken that selected salts provide a known percentage of available element(s).

Trace Minerals and Microminerals

Microminerals are elements that are generally needed by dogs and cats in less than 100 mg/Mcal amounts. These trace nutrients or minerals are generally provided from the consumption of liver or entire prey in nature, but supplementation is more common in commercial pet food. Most of these nutrients are provided as inorganic salts, but chelated forms bound to amino acids and peptides do exist. These chelated forms are typically more bioavailable and may be better tolerated than certain inorganic forms (e.g., iron proteinate versus iron sulfate).

Vitamins

Water Soluble

For dogs and cats, the only essential water-soluble vitamins are B vitamins because the animals are able to endogenously synthesize vitamin C from glucose, unlike humans. Sources of B vitamins include internal organs, the germinal portion of grains, and yeasts. Vitamin B12 is the exception because it must come from animal sources. Since B vitamins can generally be eliminated in urine, there are generally no set maximums or safe upper limits (SUL), although high doses of niacin can cause "flushing" due to prostaglandin-induced vasodilation. Vitamin C is commonly used in natural pet foods as an antioxidant for potential benefits within the body as well as a component in natural preservation systems to "recharge" mixed tocopherols used to prevent fat oxidation/rancidity. Excessive dietary vitamin C is raised as a concern in patients with a history of calcium oxalate urolithiasis since it can increase urinary oxalate excretion (Baxmann et al. 2003). Vitamin C is mainly provided in a purified form, but rich natural sources include fruits and vegetables.

Fat Soluble

For dogs and cats, the fat-soluble vitamins A, D, and E are essential. Vitamin K, although essential, can typically be provided in adequate amounts by gut floral production. An exception to this is when a diet high in fish is consumed by cats (Strieker et al. 1996). The exact mechanism by which a vitamin K deficiency is created is unknown, but Dr. James Morris, professor emeritus at the University of California, Davis, has suggested that it could be due to the high levels of vitamin E in fish (personal communication), which delays oxidation of vitamin K hydroquinone, or vitamin E acting as a competitive inhibitor of vitamin K. Cat foods rich in fish (> 25% fish on a dry matter basis) are currently required by states that adopt Association of American Feed Control Officials (AAFCO) guidelines (see Chapter 5) to add vitamin K3 or menadione and not the natural form

vitamin K1 or phylloquinone found in foods such as green leafy vegetables. Occasionally, the safety of oral menadione supplementation is raised as a concern, but the basis of these concerns is not supported by the published literature as only parenteral delivery can be harmful (NRC 2006).

Vitamin A can be produced from carotenoids such as beta carotene present in orange- or red-colored fruits and vegetables such as carrots as well as in green leafy vegetables. Cats, however, are unable to efficiently perform this conversion efficiently so their diet must contain active vitamin A or retinol. Hypervitaminosis A can occur when large amounts of liver are consumed (as discussed later in this chapter).

Some references still suggest that if the skin of dogs and cats is exposed to light, rather than being shaded by hair, the animals have the capability to synthesize adequate amounts of vitamin D. This is not true (Hazewinkel et al. 1987; Morris 1999). Typically vitamin D3 (aka cholecalciferol) is supplemented in pet food and is typically derived from lanolin from sheep's wool. Vitamin D3 is inactive as it is unhydroxylated; the hydroxylated active form is called calcitriol (1,25-dihydroxyvitamin D3). The richest natural sources of vitamin D are fatty fishes.

"Mixed tocopherols," which contain different isomers, are used in commercial pet foods to protect against oxidative damage to fat. They do not provide the same relative activity as alpha tocopherol or what is frequently referred to as "vitamin E" (i.e., beta 1/2, delta 1/10, gamma 1/10 the activity of alpha). Therefore, any guarantees for vitamin E (which is really a family of eight antioxidants) amounts should be representative of the biologically active portion of all "tocopherols" and "tocotrienols" present. Occasionally, "natural" vitamin E is suggested as being superior for supplementation, which is based on the fact that D-alpha-tocopherol has about twice the biological activity of synthetic DL-alpha-tocopherol. Obviously, this difference in biological activity can be corrected for by making adjustments in dosing when using synthetic versus natural alpha tocopherol. Good natural sources are seeds, the germ portion found in whole grains, vegetable oils, and green leafy vegetables.

Storage Pools for Essential Nutrients

Unfortunately, malnutrition can affect veterinary patients whether they are in developed or developing regions. As such it is important to briefly discuss the concept of nutrient storage pools. The body's main focus for storage is energy in the form of glycogen, which is rapidly depleted within a matter of hours, and fat, which can last patients days to weeks depending on adiposity. Along with fat, fat-soluble vitamins can be deficient in a patient's diet for weeks to months without clinically identifiable consequences, assuming a good plane of nutrition was maintained prior to the deficient diet. Some of the macrominerals, specifically calcium and phosphorus, have stores in the form of bone, and it can take long periods (i.e., months to even years in the case of calcium) to recognize clinical manifestations of a deficient diet in an adult dog or cat. Deficiencies in water-soluble vitamins and several electrolytes like potassium can be more rapidly recognized given the lack of body storage pools. Similarly, there is no storage pool for protein or amino acids, and so deficient diets result in a breakdown of body tissues such as muscle. Therefore, incomplete and unbalanced diets that are deficient in protein, electrolytes, and B vitamins are much more likely to result in clinically identifiable problems in previously appropriately fed adults than those diets that do not have adequate amounts of fat, fatty acids, fat-soluble vitamins, and calcium. This explains the lack of apparent consequences often seen in adult patients fed diets of just cottage cheese/chicken/meat and enriched rice (enriched indicating the addition of B vitamins). In the authors' clinical experience, diets deficient in thiamin and calcium that cause clinical signs (e.g., neurological and skeletal, respectively) are the most likely to be identified in adults. Many nutritional deficiencies will appear more rapidly in growing dogs and cats fed a deficient diet due to the high demand for nutrients during growth. A more comprehensive list of nutrient deficiencies, their clinical signs, and the methods for diagnosing follows.

ESSENTIAL NUTRIENT DEFICIENCY SIGNS AND CLINICALLY AVAILABLE OR RELEVANT METHODS OF ASSESSING NUTRIENT STATUS

For detailed information the reader is referred to the *Nutrient Requirements of Dogs and Cats* from the National Research Council published by the United States National Academies in 2006.

1. **Protein:** Weight loss (or lack of weight gain if a puppy or kitten), hypoalbuminemia (albumin has a half-life of approximately 20–21 days, so it may take a while for this marker to become low), and poor coat quality may also be recognized; plus any of the clinical signs associated with specific amino acid deficiencies especially those associated with the limiting amino acids, often methionine, lysine, and tryptophan for both dogs and cats.

   RECOMMENDED TESTING: Albumin and potentially analyze diet sample for crude protein with a commercial food laboratory. If a large portion of

nitrogen is suspected to not be from protein, amino acid analysis, as well as evaluation using commercial formulation software if nutrient data are available.

a. **Amino Acids**

i. **Arginine:** In dogs, vomiting, ptyalism, muscle tremors are seen with arginine-free diets; simply deficient diets have resulted in cataracts in puppies (orotic aciduria has also been reported, but there is no readily available commercial laboratory test available). In cats, diarrhea, weight loss, food refusal, and hyperammonemia; if completely devoid (only experimentally possible) death.

RECOMMENDED TESTING: Fasted plasma amino acid sample and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

ii. **Histidine:** In dogs, weight loss, decreased hemoglobin and albumin concentrations, food refusal, lethargy. In cats, cataracts and decreased hemoglobin.

RECOMMENDED TESTING: Hemoglobin and fasted plasma amino acid sample and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

iii. **Isoleucine:** Clinical signs have only been reported for growing dogs and cats; in puppies, poor food intake and weight gain; in kittens, reddish-purple tinted crusty material around eyes, nose, and mouth, desquamation on paw pads, and incoordination.

RECOMMENDED TESTING: Fasted plasma amino acid sample and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

iv. **Leucine:** Clinical signs have been only reported for growing dogs and cats: in puppies, weight loss and decreased food intake; in kittens, weight loss.

RECOMMENDED TESTING: Fasted plasma amino acid sample and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

v. **Lysine:** Clinical signs have only been reported for growing dogs and cats: in puppies, decreased food intake and weight loss; in kittens, weight loss (in other species, graying of hair has been noted but this has not been recognized in dogs and cats).

RECOMMENDED TESTING: Fasted plasma amino acid sample and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

vi. **Methionine (spared by cystine):** In dogs, pigment gallstones and dilated cardiomyopathy (DCM) secondary to taurine deficiency, and in puppies, weight loss, swelling and reddening of the skin, necrotic and hyperkeratotic front foot pads with ulceration; in cats, severe perioral and footpad lesions, and in kittens weight loss, lethargy and abnormal ocular secretions.

RECOMMENDED TESTING: Fasted plasma amino acid sample and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available; imaging, especially for DCM, as well as whole blood and plasma taurine in dogs.

vii. **Phenylalanine (spared by tyrosine):** In dogs, reddish-brown hair coat in black dogs, and in puppies, decreased food intake and weight loss; in cats, abnormal, uncoordinated gait with the tail bending forward, ptyalism, vocalizing and hyperactivity, and in kittens, weight loss and reddish-brown hair in black cats.

RECOMMENDED TESTING: Fasted plasma amino acid sample; potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available; close inspection of any black hairs for reddish-brown tint.

viii. **Threonine:** Clinical signs only reported for growing dogs and cats; in puppies, decreased food intake and weight loss; in kittens, decreased food intake and weight loss and cerebellar dysfunction with slight tremors, ataxia, jerky head and leg movements, and difficulty maintaining equilibrium

RECOMMENDED TESTING: Fasted plasma amino acid sample and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

ix. **Tryptophan:** Clinical signs have only been reported for growing dogs and cats, although

additional tryptophan has been reported to reduce territorial aggression (DeNapoli et al. 2000); in puppies, decreased food intake and weight loss; in kittens, decreased food intake and weight loss.

RECOMMENDED TESTING: Fasted plasma amino acid sample and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available

x. **Valine:** Clinical signs have only been reported for growing dogs and cats: in puppies, decreased food intake and weight loss; in kittens, weight loss.

RECOMMENDED TESTING: Fasted plasma amino acid sample and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

xi. **Taurine:** This amino acid is required only in cats; feline central retinal degeneration and blindness, DCM and heart failure, deafness, poor reproduction with congenital defects including hydrocephalus and anencephaly can result when it is deficient; in dogs, taurine can become depleted due to insufficient dietary precursor(s), methionine (and cystine), DCM, and poor reproduction.

RECOMMEND TESTING: Fasted plasma amino acid sample and whole blood sample; potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available; fundicus examination and echocardiogram; review breeding program and health status of breeding animals to rule out other causes of poor reproductive performance.

2. Fat
   a. **Linoleic Acid (LA):** In puppies, greasy pruritic skin with keratinization with parakeratosis; in cats, dry, lusterless hair, dandruff, behavioral infertility, and hepatic lipid infiltrates; no dog or kitten clinical signs have been reported but are likely an amalgamation of the signs seen in puppies and cats.

   RECOMMENDED TESTING: Potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available; consider LA-rich oil supplementation if only a dull coat with scaling or dandruff presents; monitor for resolution for confirmation of likely LA deficiency.

   b. **Arachidonic Acid (AA; cat, not dog):** AA is not required in dogs as they have adequate activity of delta-6-desaturase to convert LA to AA, unlike cats; in cats, reproductive failure with congenital defects and low kitten viability, deficiency may manifest only after one or two successful litters.

   RECOMMENDED TESTING: Potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available; review breeding program and health status of breeding animals to rule out other causes of poor reproductive performance.

3. Minerals
   a. Macrominerals (required at ≥100 mg/Mcal)
      i. **Calcium (Ca):** In dogs and puppies, nutritional secondary hyperparathyroidism (see Chapter 10); in kittens, bone rarefaction especially of the pelvis and lumbar vertebrae; in cats, decreased bone density; in cats and kittens, nutritional secondary hyperparathyroidism.

      RECOMMENDED TESTING: Potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available; whole body radiographs ensuring that mandibular, veterbral, and pelvic bones are imaged; serum calcium concentrations are likely maintained within normal reference intervals; however, ionized calcium, PTH and vitamin D measurements may be useful.

      ii. **Phosphorus (P):** In dogs, hypophosphatemia and if severe, anemia may present; and in puppies, poor growth and hypophosphatemia (remember to compare to reference intervals for growing dogs as adults inherently have lower P concentrations).

      RECOMMENDED TESTING: Serum phosphorus concentrations and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

      iii. **Magnesium (Mg):** In dogs, hypomagnesemia, and in puppies, lameness and hyperextension of carpi; in cats, hypomagnesemia, and in kittens, poor growth, hyperextension of metacarpi, muscular twitching and convulsions.

      RECOMMENDED TESTING: Serum ionized magnesium concentrations and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

iv. **Sodium (Na):** In dogs, hyponatremia, and in puppies, dry, tacky mucous membranes, restlessness, and increased heart rate, hematocrit and hemoglobin (likely hemoconcentration), as well as polyuria and polydipsia; in cats, hyponatremia, and in kittens, anorexia, poor growth, polyuria, polydipsia, hemoconcentration.

RECOMMENDED TESTING: Serum sodium concentrations and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

v. **Potassium (K):** In dogs, hypokalemia and hypotension; in puppies, poor growth, restlessness, ventroflexion of the head, rear leg paralysis, and generalized weakness; in cats, hypokalemia and elevation in serum creatinine; in kittens, anorexia, poor growth, ventroflexion of the head, ataxia, and muscular weakness leading to the inability to walk.

RECOMMENDED TESTING: Serum potassium concentrations and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

vi. **Chloride (Cl):** Clinical signs have only been reported for growing dogs and cats; in puppies, hypochloremia, hypokalemia, and metabolic acidosis, poor growth, weakness, ataxia (potentially due to concurrent potassium deficiency); in kittens, hypokalemia.

RECOMMENDED TESTING: Serum chloride and potassium concentrations and potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

b. Microminerals (required at < 100 mg/Mcal)

i. **Iron (Fe):** In dogs, microcytic hypochromic anemia and a low percentage saturation of plasma transferrin, and in puppies, low hemoglobin concentrations and hematocrit, poor growth, pale mucous membranes, lethargy, weakness, diarrhea, hematochezia, and melena.

RECOMMEND TESTING: Complete blood count and total iron-binding capacity (TIBC) and if available, plasma ferritin along with percent saturation; reticulocyte indices may also be worth exploring even though there is some debate about their value, and they may not be clinically available (Steinberg and Olver 2005; Fry and Kirk 2006); potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

ii. **Copper (Cu):** In dogs, no clinical signs reported, and in puppies, loss of hair pigmentation and hyperextension of the distal phalanges; in cats, increased time to conception in queens, and, in kittens, fading coat color, hindlimb ataxia, twisted limbs, and curled tails.

RECOMMENDED TESTING: Liver biopsy is considered the gold standard, but if it is not practical, consider serum or plasma copper in dogs (not reflective of status in cats); potentially analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available. If the sole source of copper supplementation is cupric oxide, this may increase suspicion as this form has very poor bioavailability.

iii. **Zinc (Zn):** In dogs, skin lesions, and in puppies, very poor growth rates, skin lesions starting at contact or wear points like foot pads (also see Chapter 11); in cats, no clinical signs reported, and in kittens, poor growth and skin lesions.

RECOMMENDED TESTING: Plasma zinc and analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

iv. **Manganese (Mn):** In dogs and cats, there are no reports of clinical signs seen with manganese deficiency (there are reports in other species suggesting bone and joint abnormalities).

RECOMMENDED TESTING: Consider whole blood manganese analysis; analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

v. **Selenium (Se):** In dogs, cats, and kittens, there are no reports of clinical signs; in puppies, anorexia, depression, dyspnea, and coma.

RECOMMENDED TESTING: Consider erythrocyte GPx activity and selenoprotein P analysis (be prepared to provide normal control samples) or serum selenium; analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

vi. **Iodine (I):** In dogs and puppies, goiter/enlarged thyroid gland, alopecia, dry coat,

weight gain, and sometimes reduced thyroid hormone; in cats and kittens, no clinical signs have been seen but at necropsy enlarged thyroid tissue has been seen.

RECOMMENDED TESTING: Thyroid hormones (not conclusive) or urinary iodine excretion and analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

4. Vitamins
   a. Fat-Soluble Vitamins
      i. **Vitamin A (retinol only in cats; if vitamin A is needed in dogs, they can convert beta-carotene to vitamin A):** In dogs and puppies, anorexia, weight loss, ataxia, xerophthalmia ("dry eyes"), conjunctivitis, corneal opacity and ulceration (likely due to xerophthalmia), skin lesions, and deafness; in cats, conjunctivitis, xerosis (specifically dry conjunctiva) with keratitis and vascularization of the cornea (likely due to the xerosis), photophobia, delayed papillary response to light, cataracts, abortions and premature birth; in kittens, the signs seen in cats, plus hairlessness and cleft palates.

      RECOMMENDED TESTING: Schirmer tear test (not conclusive); plasma retinol (laboratory availability unknown); analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

      ii. **Vitamin D:** In dogs and cats, there are no reports of clinical signs; in puppies, lethargy, poor muscle tone, large swellings at the epiphyseal ends of bones, bending of long bones, and osteopenia on radiographs; in kittens, reluctance to move, progressive caudal paralysis, sometimes enlargement of the metatarsal joints, poor food intake, weight loss, hypocalcemia, elevated parathyroid hormone (PTH).

      RECOMMENDED TESTING: Serum 25-OHD, PTH, serum calcium and ionized calcium (in kittens); radiographs (consistent with "rickets", see Chapter 10); analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

      iii. **Vitamin E:** In dogs and puppies, dermatosis, degeneration of skeletal muscles, muscle weakness, reproductive failure, retinal degeneration, subcutaneous edema, anorexia, depression, dyspnea, and coma; in cats (and presumably kittens), depression, anorexia, hyperesthesia on palpation of the ventral abdomen and nodular adipose tissue (also known as steatitis or yellow fat disease).

      RECOMMENDED TESTING: Physical examination (plus biopsy of nodules); plasma alpha-tocopherol (laboratory availability unknown; possibly dialuric acid hemolysis assay but likely clinically unavailable); analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

      iv. **Vitamin K:** In dogs and puppies, prolongation of clotting times and excessive bleeding only achievable with the use of anticoagulants (e.g., coumarin, a "vitamin K antagonist"); in cats and kittens, excessive bleeding, prolonged clotting times, increased proteins induced by vitamin K antagonism or absence (PIVKAs); high fish diets can induce a vitamin K deficiency as noted earlier in this chapter. (Note: the Devon Rex breed can have a genetic defect that causes a deficiency of all vitamin K-dependent blood coagulation factors.)

      RECOMMENDED TESTING: Prothrombin time (PT); partial thromboplastin time (PTT); PIVKA test; possibly analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

   b. Water-Soluble Vitamins
      i. **Thiamin, vitamin B1:** In puppies (and presumably in dogs), inappetance, failure to grow, weight loss, coprophagia, neurological signs (e.g., CNS depression, sensory ataxia, paraparesis, torticollis, circling, tonic-clonic convulsions, muscular weakness, recumbency), and sudden death; in cats, bradycardia, anorexia, neurological signs (i.e., posture changes, short tonic convulsive seizures), progressive weakness prostration, and death; in kittens, mydriasis, ataxia, and erect tails; ventroflexion of the head and bradycardia have also been reported. It should be noted that along with taurine and calcium deficiency this is the other common nutritional deficiency that the authors have recognized in multiple clinical patients in a tertiary referral setting.

      RECOMMENDED TESTING: Erythrocyte transketolase activity; thiamine phosphorylated esters in plasma (reported to be more sensitive than erythrocyte transketolase, laboratory unknown); CNS imaging [i.e., magnetic resonance, although the use of computed

tomography has been reported in humans (Swenson and St. Louis 2006)]; analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

ii. **Riboflavin, vitamin B2:** In dogs (presumably puppies as well), anorexia, weight loss, muscular weakness, ataxia, ocular lesions described as opacity of the corneas, sudden collapse to a semicomatose state, and death; in cats (presumably kittens as well) anorexia, weight loss, periauricular alopecia, cataracts, and testicular atrophy.

RECOMMENDED TESTING: Erythrocyte glutathione reductase activity coefficient (EGRAC; laboratory availability unknown) and analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

iii. **Pyridoxine, vitamin B6:** In dogs, convulsions, muscle twitching, and microcytic hypochromic anemia, and in puppies, anorexia, weight loss, and death; in cats (presumably kittens as well), growth depression, mild microcytic hypochromic anemia, convulsive seizures, and calcium oxalate crystalluria.

RECOMMENDED TESTING: CBC; urinalysis; plasma tyrosine (it can be elevated as the first enzyme for tyrosine degradation can be depressed); analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

iv. **Niacin, vitamin B3:** In dogs (presumably puppies as well), anorexia, weight loss, reddening of the inside of the upper lip that progresses to inflammation and ulceration, vermilion bands on the lips, ptyalism with thick, blood-stained saliva, bloody diarrhea, and eventually death (historically described as "black tongue" and compared to pellagra in humans); in cats and kittens, anorexia, fever, fiery red tongue with ulceration (not always), weight loss, respiratory disease and death.

RECOMMENDED TESTING: Nicotinamide loading test (laboratory unknown); analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

v. **Pantothenic Acid, vitamin B5:** In dogs and puppies, poor food intake, sudden prostration or coma, tachypnea, tachycardia, convulsions, gastroenteritis, and intussusceptions; in cats, no reports; in kittens, poor growth.

RECOMMENDED TESTING: Analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

vi. **Cobalamin, vitamin B12:** In dogs and puppies, inappetance, neutropenia with hypersegmentation and megablastic anemia; in cats, no obvious clinical signs have been reported; in kittens, anorexia and "wet" hair coat (cobalamin deficiency has been reported secondary to inflammatory bowel disease and bacterial overgrowth; deficiency is also possible if the ileum has been resected, as that is the site of absorption).

RECOMMENDED TESTING: Serum cobalamin; CBC; analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

vii. **Folic Acid, vitamin B9:** In dogs and puppies, cleft palates (in Boston Terrier puppies) decreased growth rate, decreased hemoglobin and hematocrit; in cats, no reports; in kittens, decreased growth rate.

RECOMMENDED TESTING: Serum folate; CBC (the "Formiminoglutamic or "FIGLU" test has been used in research environments); analyze a diet sample as well as evaluate using commercial formulation software if nutrient data are available.

viii. **Biotin, vitamin H or B7:** In dogs, hyperkeratosis; in cats, no reports; in kittens, accumulation of salivary, nasal, and lachrymal secretions, alopecia, loss of hair pigment, weight loss, and diarrhea.

RECOMMENDED TESTING: Dietary history of feeding raw eggs or egg whites (which contain the protein "avidin," which binds biotin) as this appears to be the only way to create a deficiency.

ix. **Choline:** In dogs, weight loss, hypocholesterolemia, vomiting, fatty liver, and death; in kittens, decreased food intake, and decreased growth rate.

RECOMMENDED TESTING: Plasma choline and phosphatidylcholine; analyze diet sample for all methyl group donors (i.e., choline, betaine, and methionine in excess of

the amino acid requirement); evaluate using commercial formulation software if nutrient data are available.

Diagnostic and Food Analysis Laboratories and Diet Computer Analysis

As can be seen from the list above, samples may need to be submitted to laboratories for the diagnosis of certain nutritional deficiencies. The most common nutrients analyzed in veterinary patients are taurine, calcium/vitamin D, electrolytes (i.e., phosphorus, sodium, potassium, magnesium, chloride), iron (via TIBC), vitamin K (via PIVKA), thiamin, cobalamin (vitamin B12), and folate. Many of these nutrients may be analyzed in the normal course of working up a case and may be familiar to the veterinary practitioner. Others may be more exotic or available only through a research laboratory. For the reader's convenience the following laboratories are suggested (note these are all in the United States given the authors' geography and are current as of 2010):

- Eurofins Scientific, Inc., Des Moines, IA, (515) 265-1461, for food analysis
- Midwest Laboratories, Omaha, NE, (402) 334-7770, for food analysis
- UC Davis Amino Acid Laboratory, Davis, CA, (530) 752-5058, for amino acid and trace mineral analysis from patients and diets (run by one of the authors, AJF)
- Michigan State University Diagnostic Center for Population and Animal Health (DCPAH), Lansing, MI, (517) 353-1683, for vitamin D metabolites and PTH in patients
- Texas A&M GI Lab, College Station, TX, (979) 862-2861, for cobalamin and folate

Other tests may be available via national commercial veterinary diagnostic laboratories such as IDEXX Laboratories and ANTECH Diagnostics.

As some tests may not be available, analysis of a diet via computer analysis may be useful. Any such analysis is only as good as the nutrient database that is used. Certain nutrients of interest are not always reported or there can be large variations in the range of values seen with foods; therefore, such analyses must be used as supportive or suggestive only. Commercial formulation software used by pet food companies (Concept 5 Formulation System, www.agri-data.com) is typically too complex and expensive for even veterinary academicians and does not come with preloaded nutrient data for foods or ingredients. Software used for livestock (e.g., Dalex Livestock at www.dalex.com) is generally too cumbersome to adapt to dogs and cats from swine modules. Two web-based software programs, Food Processor (available at www.esha.com) and Balance IT (available at www.balanceit.com), are known to the authors as being used by veterinary nutritionists and veterinarians. The latter program, Balance IT, is designed specifically for veterinary use and was created by one of the authors (SJD). Both of these programs rely heavily on the USDA Nutrient Database for Standard Reference at http://www.nal.usda.gov/fnic/foodcomp/search/, which has an extensive database of human foods; certain nutrients of interest, however, such as taurine, chloride, iodine, and vitamin D are typically not available. Therefore, "deficiencies" in these nutrients suggested by computer analysis when compared to reported nutrient requirements for dogs and cats may be the result of a lack of available data rather than a real deficiency (this can also be true of choline, which is not routinely reported by the USDA).

NUTRIENT REQUIREMENTS

Nutrient requirements are available from two main references, the annually published *Official Publication* of the Association of American Feed Control Officials (AAFCO), whose assembled experts largely base the "AAFCO nutrient profiles" on the *Nutrient Requirements of Dogs and Cats* from the National Research Council (commonly referred to as the "NRC") published by the United States National Academies. The most recent NRC requirements, published in 2006 (approximately 20 years after the previous version), have not yet been incorporated into the 2011 AAFCO profiles. Most nutrient requirements have not vastly changed with the publication of the 2006 NRC, but the NRC has suggested requirements for several omega-3 fatty acids (e.g., EPA, DHA, and ALA), and a few amino acid and mineral levels have shifted.

Nutrient requirements from AAFCO are provided as "minimum" and "maximum" levels for "growth and reproduction" and "adult maintenance" on both a dry matter basis and a "per 1,000 kcal ME," or energy basis. The nutrient profile on an energy basis is used for more energy dense foods [i.e., > 4,000 kcal ME/kg dry matter (DM) food for dogs and > 4,500 kcal ME/kg DM for cats]. This ensures that adequate amounts of nutrients are consumed, since dogs and cats eat to their caloric need as discussed earlier in the chapter. The profile on a dry matter basis essentially ensures that if an animal is eating a less energy-dense diet, the volume of food it will need to eat to meet its nutrient requirements is physically possible. Certain nutrient minimums also change depending on the food.

Different recommendations are provided for copper and taurine for foods that are extruded versus canned. The recommendations for vitamin K are higher if the product contains a high fish content. Maximums are provided for select nutrients and are the same regardless of life stage.

The NRC provides separate requirements for growing and reproducing dogs and cats. Additionally, three different "minimal" requirements are provided instead of just one as with the AAFCO profiles, along with a safe upper limit (SUL), which is potentially different for every life stage (unlike with AAFCO). The three different "minimal" requirements in the NRC are minimal requirement, adequate intake, and recommended allowance. The minimal requirement (MR) is defined as "the minimal concentration or amount of a bioavailable nutrient that will support a defined physiological state." This requirement assumes that 100% of the nutrient is available; therefore, it does not account for, say, poor digestibility or antagonisms that can frequently occur with amino acids, minerals, and fat-soluble vitamins. The adequate intake (AI), which is defined as "the concentration in the diet or amount required by the animal of a nutrient that is presumed to sustain a given life stage when no MR has been demonstrated." This value is used when graded studies were not available or when comparative data had to be relied on. Recommended allowance (RA) is defined as "the concentration or amount of a nutrient in a diet formulated to support a given physiological state." This requirement is most analogous to the AAFCO minimum as both requirements attempt to insert a safety factor to account for uncertain bioavailability. The NRC also uses an additional unit not used by AAFCO. The unit of amount per kilogram body weight raised to the 3/4 power (i.e., Amt./kg $BW^{0.75}$) is also provided by the NRC, which is more analogous to the "dosing" of medications. This third method of expressing requirements is not as commonly used by nutritionists, who generally think about the nutrient concentrations needed in foods rather than a "dose" for a particular patient. The reader is directed to Chapter 6 for further discussion on units for expressing nutrient levels and comparing values provided in different units.

KEY CLINICAL NUTRITIONAL EXCESSES AND SIGNS

Beyond calcium and vitamin D excess and related orthopedic or renal consequences (covered later in the text), the main nutrient excesses of clinical significance are vitamin A and methionine. Hypervitaminosis A can occur clinically when an all- liver diet (or a mainly liver diet) is fed to kittens that leads to extensive osseocartilagenous hyperplasia of the first three cervical vertebrae. These changes restrict movement and result in an unkempt coat as the affected cat cannot groom itself. Methionine excess can result in a hemolytic anemia with methemoglobinemia with Heinz body formation. However, the risk appears to be associated with purified amino acid supplementation, not with the consumption of intact dietary protein. From NRC 2006: "… and it would be predicted that peptide-bound methionine in protein would be less toxic than that provided in the free form. Thus, it is unlikely that cats eating natural prey would exceed the SUL for methionine." The authors have not recognized methionine toxicity in cats that eat essentially all-meat diets, even when the protein content was quite high (at 50% protein calories). Several other nutrients have maximum values set by AAFCO due to concerns of antagonism, but these are generally clinically less important, with the exception of zinc excess, which is discussed in the text's hepatobiliary chapter's discussion on the management of copper storage disease.

ADDITIONAL EDUCATION ON NUTRITION

Inherently this chapter's coverage of basic nutrition is limited; therefore, readers with a greater interest in basic nutrition as well as nutrition in general are referred to the following resources (roughly listed in increasing level of intensity or depth):

- American Academy of Veterinary Nutrition (AAVN) Listserv (www. aavn.org, annual membership fee required)
- General nutrition or biochemistry texts
- Veterinary medical school/college coursework (often available to the public through "open campus" or "extension" programs)
- Continuing education [diplomates of the American College of Veterinary Nutrition (DACVN) actively present at regional, national, and international meetings (e.g., U.S., Canada, U.K., Australia, New Zealand), as do European diplomates
- Internship/externship (available with numerous DACVNs)
- Fellowships (some universities host veterinarians such as UC Davis through the Donald G. Low-CVMA Practitioner Fellowship)
- Graduate courses in nutrition (aimed at master's and/or PhD students; may require enrollment)
- Veterinary nutrition residency training (see the American College of Veterinary Nutrition www.acvn.org); these 2- to 4-year programs are currently available at a variety of veterinary medical institutions

Readers are encouraged to explore these additional resources to build on their knowledge of nutrition, and it is hoped that this text will play a supportive role if any of these additional learning opportunities are undertaken.

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Determining Energy Requirements

3

Jon J. Ramsey

INTRODUCTION

Determining the energy requirements of an individual patient is a challenge for any nutritionist or veterinarian. Animals require a very specific amount of energy to maintain a given body weight, and even slight deviations from this requirement can induce weight gain or loss. To determine the amount of food required by an animal, it is necessary to know the animal's energy requirement and the energy content of the foods offered to the animal. There are a number of equations available to predict either energy requirements or the amount of energy in foods. However, a number of assumptions typically need to be made when using these equations, and it is important to realize the limitations of commonly used equations. It should be stressed that predicted energy requirements should be viewed as an "educated guess" at the animal's true energy requirement. These equations should be used as a tool to provide a starting point for selecting the amount of food to give an animal, and adjustments should be made based on any observed changes in body weight. The purpose of this chapter is to provide the background necessary to estimate energy requirements for dogs and cats and calculate the energy content of foods.

Units

Energy is frequently defined as the capacity to do work. This definition applies equally to the physical or biological sciences, and similarly the same basic units of energy are used in all branches of science. In the United States, the most common unit of energy used in nutrition is the calorie. This calorie is defined as the amount of heat required to increase the temperature of water from 14.5°C to 15.5°C. This is sometimes referred to as the "15°C calorie," "small calorie," or "gram-calorie." A calorie is a very small unit of energy, and the unit typically used for dog and cat nutrition is the kilocalorie. The kilocalorie (kcal) is equivalent to 1,000 calories, and it is sometimes called the "kilogram-calorie," "big calorie," or "Calorie" (written with an uppercase "C"). This last term is commonly used in human nutrition, and it is very important to note that the Calorie listed on labels for human foods is actually a kilocalorie. The kilocalorie is the energy unit primarily used in dog and cat nutrition, although the megacalorie (Mcal), equivalent to 1,000,000 calories or 1,000 kilocalories, is also occasionally used.

Although the kilocalorie is still widely used in the United States, the joule is actually the designated SI unit of energy. Conversion between calories and joules can easily be accomplished using the following equation:

$$1\,\text{calorie} = 4.184\ \text{joules}$$

The joule (J) is a small amount of energy, and therefore, the kilojoule (kJ, equal to 1,000 J) and megajoule (MJ, 1,000,000 J or 1,000 kJ) are the units most commonly used in animal nutrition.

Animal energy requirements are given as an amount of energy per unit of time. The watt (1 J/sec) is a unit that is frequently used in the physical sciences and exercise physiology to indicate rate of work or energy expenditure. However, the watt is not commonly used in nutrition, and

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energy requirements for dogs and cats are often given as kcal/day or kJ/day.

The energy content of food is generally expressed as the amount of energy per unit of weight or volume. Energy per unit of weight is typically used in equations for calculating diet energy content, and it is preferable to convert food intake measured in units of volume to units of weight (grams or kilograms). This is best accomplished by weighing a given volume of the food, since there is no standard equation for converting volume to weight. The weight of a volume of food will depend on the density of the food, which can be highly variable.

Basic Concepts and Terminology

The laws of thermodynamics form the foundation for the study of energy metabolism. In particular, the first law of thermodynamics is central to all systems for predicting animal energy requirements. This law indicates that energy can neither be created nor destroyed, but can simply change from one form to another (Haynie 2001). Thus, energy metabolism in animals can be viewed as an accounting exercise, since the energy consumed by the animal must appear in tissue macromolecules (i.e., fat, protein, or glycogen) or leave the body as energy expenditure or excreta. Animal energy requirements are often described in terms of energy balance.

Energy balance is defined as the mathematical difference between energy intake and energy expenditure. An animal is in a state of energy balance (i.e., body energy stores are constant) if the amount of energy consumed matches the amount of energy expended by the animal. If energy intake exceeds energy expenditure, the animal enters a state of positive energy balance and net retention of energy leads to an increase in body weight. Similarly, if energy intake is less than energy expenditure, the animal enters a state of negative energy balance and net loss of body energy leads to weight loss.

The **maintenance energy requirement** is the amount of energy required to maintain an animal in a state of energy balance, or in other words, the amount of energy needed to maintain an animal at its current weight (and body composition). It is typical to predict the maintenance energy requirement for a dog or cat and then make adjustments to this value if weight loss or weight gain is desired.

As a first step toward determining energy requirements, it is important to understand the terminology that is commonly used in energy metabolism. A number of terms are used to describe the energy intake and energy expenditure of an animal (Wenk et al. 2001). The following terms describe the energy available to the animal after accounting for various sources of energy loss (Fig. 3.1).

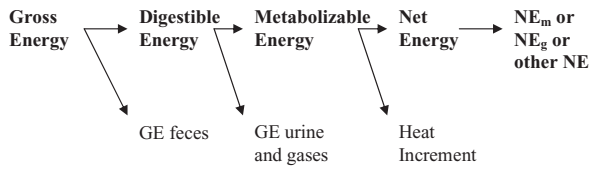

Fig. 3.1. Energy terms and sources of energy loss in animal nutrition.

Gross energy (GE) is the amount of heat that is released from a given amount of food following complete combustion in a bomb calorimeter. Gross energy is a physical rather than biological measure and represents the maximum energy of a diet or feedstuff. Another term for gross energy is "heat of combustion." Gross energy gives little information about the energy available to the animal since foods are not entirely digested and energy is lost in feces, urine, and as heat produced during the digestion and assimilation of dietary nutrients. **Digestible energy** (DE) is the energy remaining after subtracting the gross energy of feces from the gross energy of food:

$$DE = GE_{food} - GE_{feces}$$

DE energy is a measure of the "apparent" digestible energy, since the feces contains energy from products other than food (e.g., digestive enzymes, sloughed cells from the gut, mucus, etc.). Energy requirements for horses are given as DE, but this term is rarely used in dog and cat nutrition. **Metabolizable energy** (ME) is the energy remaining after subtracting the gross energy of urine and the gross energy of gaseous products of fermentation from DE:

$$ME = DE - GE_{urine} - GE_{gas}$$

Energy requirements for dogs and cats are primarily given in terms of ME. **Net energy** (NE) is the energy remaining after subtracting heat increment (heat production associated with the consumption of food) from ME:

$$NE = ME - \text{heat increment}$$

Net energy includes energy that may be used for either maintenance of the animal or production (i.e., growth, lactation, reproduction). Energy requirements for agricultural species are often given in terms of NE, and there is currently not sufficient information to accurately provide energy requirements for dogs or cats in terms of NE.

Energy expenditure at maintenance is composed of four basic components: (1) resting energy expenditure, (2) activity-related energy expenditure, (3) heat increment, and (4) facultative thermogenesis. Energy requirements can be determined by measuring energy expenditure, and energy requirements are often given in relation to resting (or basal) energy expenditure with adjustments made for other components of total energy expenditure. Resting energy expenditure is typically the largest component of total energy expenditure and frequently accounts for greater than 50% of energy expenditure. The following terms are frequently used to describe this component of energy expenditure:

Basal metabolic rate or **basal energy expenditure** is a term that applies primarily to human nutrition and physiology because the conditions required to measure basal metabolic rate are so stringent that it is virtually impossible to complete these measurements in animals. Basal metabolic rate is energy expenditure measured in a postabsorptive state under thermoneutral conditions (i.e., no additional energy expenditure is required specifically to maintain body temperature) with the subject lying but awake and in complete muscular repose. The subject should also be free from emotional stress.

Because it is difficult to have an animal cooperate with all of these conditions, the term **resting energy** (or **resting metabolic rate**) is more often used in animal nutrition. Resting energy expenditure is measured in animals that are lying down. Resting energy expenditure is often measured in animals that are not fasting, and therefore it may contain some energy associated with the digestion of food.

Fasting energy expenditure (or **fasting heat production**) is measured in animals that are denied access to food. These measurements are generally completed in animals that have been fasted for a sufficient duration to ensure that no food remains in the gastrointestinal tract. Many of the original equations for predicting maintenance energy requirements were derived from measures of fasting energy expenditure. These measurements were completed using calorimetry systems that allowed limited movement for the animals, and thus these measures are generally only slightly higher than basal energy expenditure.

Activity-related energy expenditure is the energy expenditure associated with muscular exercise. The energy expenditure associated with physical activity is highly variable both between animals (working dog vs. a sedentary apartment-dwelling dog) and within the animal (day of intense work vs. day of rest). A rough measure of physical activity can be obtained by dividing 24-hour energy expenditure by resting energy expenditure. For a sedentary animal, these values will be similar, and the ratio will be less than 1.5, while for an active athlete this ratio will be 2.0 or greater.

Heat increment is the energy expenditure associated with ingestion, digestion, assimilation, and metabolism of food. Heat increment is also called **thermic effect of feeding**, **diet-induced thermogenesis**, or **meal-induced thermogenesis.** Heat increment is responsible for 10–15% of total daily energy expenditure in many simple stomached animals (Blaxter 1989), and it likely contributes a similar percentage to energy expenditure in dogs and cats. The magnitude of heat increment is dependent on both meal size and the nutrient composition of the meal. As expected, heat increment is zero in fasted animals, and heat increment tends to increase in proportion to the amount of energy consumed in a meal. Heat increment is greatest for dietary protein followed by carbohydrate and fat. The high heat increment of protein is sometimes given as one of the reasons for including relatively high amounts of protein in weight loss diets.

Facultative thermogenesis is a term used to describe the increase in energy expenditure associated with cold or heat stress (and occasionally other forms of stress). This is the energy expenditure required to maintain body temperature when an animal is outside its thermoneutral zone (the temperature range where the previously mentioned components of energy expenditure are sufficient to maintain body temperature). The thermoneutral zone for adult dogs has been reported to lie between 20°C and 25°C and 30°C and 35°C (NRC 2006), although the exact thermoneutral zone for a given dog will depend on breed, coat length, and adaptation time to a particular ambient temperature. For cats, the thermoneutral zone is not entirely known although it has been estimated to lie between 30°C and 38°C (NRC 2006). Facultative thermogenesis will be increased in dogs and cats exposed to temperatures either above or below their thermoneutral zones, and it is often considered to be a relatively small component of energy expenditure in animals that live indoors and do not experience prolonged exposure to very cold or warm temperatures. However, facultative thermogenesis can be a major contributor to energy expenditure in dogs or cats that live outdoors and experience temperatures well outside their thermoneutral zone.

Energy requirements for dogs and cats are typically given as metabolizable energy at maintenance. The terms described in the preceding paragraphs are occasionally mentioned when it is necessary to adjust maintenance energy (ME) requirements for changes in ambient temperature or physical activity.

DIET RECORDS OR HISTORY

An accurate diet record or history is the best way to determine the ME requirement for an animal that is weight stable and maintaining a constant body condition score. This reflects the fact that the animal is currently selecting (or the owner is feeding) the appropriate amount of energy needed to maintain constant body weight. The task now becomes to determine the amount of ME being consumed from the information supplied by the owner. To accomplish this task, it is essential to have detailed and accurate information about all food sources being offered to the animal. To estimate ME intake, a diet record should contain the following information:

1. The type of food consumed by the animal (i.e., brand and product information for commercial diets, food ingredients for home cooked diets, etc.).
2. The amount of food offered to the animal (preferably given in weight, but from a practical standpoint this information is more often available as volume of food).
3. The type and amount of treats offered to the animal (i.e., brand and product information for commercial treats, human foods used as teats, and amount of each food treat typically consumed).
4. The type and amount of nutritional supplements given to the animal.
5. The type and amount of "table scraps" commonly given to the animal.

A diet record should also provide information on the daily variation in energy intake. For animals that consume the same diet each day, estimates of ME intake can be made from information provided for a typical day. In contrast, information from several days to over a week may be required to reasonably estimate ME intake in an animal that experiences daily variation in the type and amount of food that it consumes.

In addition to information about the composition and amount of food consumed, it is also important that the diet record include information that will determine the ability of the owner to properly monitor and control the animal's energy intake. This information should include:

1. The feeding strategy used with the animal. Is the animal given free choice consumption of food or is it given food in discrete meals?
2. The number of other pets in the household. Does the animal eat alone or does it have access to food offered to other pets? Do other pets have access to the animal's diet?
3. The number of people feeding the animal. Does only one person feed the animal or do multiple people give the animal food, including treats?
4. The housing conditions for the animal. Does the animal live indoors or does it spend some time outside? If the animal is outside, does it have access to food or people who may offer it food?

The inclusion of this information on the diet record will help determine if a reasonable estimate of ME intake is possible. While diet records provide the best way to determine the ME requirement for maintenance in a dog or cat, there are also several key limitations that need to be considered when calculating ME from diet records. First, it has been noted that many owners are not particularly accurate when reporting food intake for their pets (Hill 2006). This is not surprising since it has been widely reported that human volunteers tend to underestimate their own energy intake when using diet records. Second, owners often use measures of volume to quantify the amount of food offered to their pets, while measures of weight are generally used for calculating ME. Whenever possible, food scales should be used to help assign a weight to the volume of food given to the animal. Third, all owners do not use uniform measuring devices for determining the amount of food given to their animals. What one owner considers a "cup" may be very different from what another owner uses as a cup. The use of weight, rather than volume, removes this source of error. Fourth, owners may not always be precise in measuring the volume of food given to the animal. A heaping cup may be listed as a cup on a diet record, and accuracy needs to be stressed when completing a diet record.

Despite the limitations of diet records, an attempt should be made to estimate ME intake at maintenance using diet records prior to calculating maintenance energy requirements using standard equations. Accurate diet records are still the best method available to calculate the maintenance energy requirements of an individual animal.

CALCULATING ENERGY CONTENT OF A DIET

It can be a challenge to determine the energy content of dog and cat foods. This reflects the fact that commercial dog and cat foods often do not contain calorie information on their labels. Also, dogs and cats may be fed human foods for which energy information is not readily available. Thus, some knowledge of basic energy calculations is needed to provide an estimate of the energy content of specific foods or complete diets. Energy calculations are used to convert the measures of food intake included in a

diet record into values of energy intake (kcal or kJ per day). This information may then be used to calculate the ME requirement for an animal. Energy calculations are also used to simply estimate the energy content of a diet and allow comparisons of energy content between diets.

There are several ways that the energy content of a food or diet can be either determined or calculated. One way is simply to determine if the food comes in packaging that contains energy information. Packaged human foods are required to contain energy information, and some commercial pet foods also will have this information on the label. In the case of human foods, the USDA National Nutrient Database for Standard Reference (www.nal.usda.gov/fnic/foodcomp/search) may also be searched for energy information of foods when labels that contain energy information are not readily available.

It is also possible to obtain energy information for commercial dog and cat foods by contacting the company that produces the food. Many companies have energy information available on their websites, along with the guaranteed analysis of the diet. Companies will also generally provide energy information if contacted by a consumer.

All energy information provided on labels, websites, or databases is obtained either from direct experiments or calculations using standard values for energy. Experiments that measure the energy content of diets are the most accurate way to determine energy but also the most expensive and time consuming. Some companies use feeding experiments to determine the ME content of their diets, and the Association of American Feed Control Officials (AAFCO) publishes protocols (AAFCO 2007) that need to be followed if a company wishes to report ME values obtained from these experiments. To understand the source of values used for calculating ME, it is important to have some knowledge of the steps involved in using feeding experiments to determine ME. A typical protocol for determining diet ME includes the following steps:

1. GE (kcal or kJ per gram) is determined for the diet by bomb calorimetry.
2. The animal is adapted to the diet and the environment where the experiment will be completed. In the AAFCO protocol (AAFCO 2007), the animal is fed the diet for at least 5 days prior to the start of feces (and possibly urine) collections. During this time, it is important to make certain that the animal is consuming an appropriate amount of food to maintain weight.
3. All feces (and possibly urine) are collected and weighed over at least a 5-day period. Food intake is also carefully determined during this time. The collected feces is pooled and mixed, and a representative sample is taken for determination of GE by bomb calorimetry. If urine is collected, the urine is combined and an aliquot is taken for determination of GE by bomb calorimetry.
4. ME is calculated using one of the following equations:

Equation A: used when both feces and urine are collected.

$$\text{ME (kcal/kg)} = \frac{(FI \times GE_{food}) - (F \times GE_{feces}) - (U \times GE_{urine})}{FI} \times 1000$$

FI = food intake (g)
GE_{food} = gross energy of the diet/food (kcal/g)
F = amount of feces collected (g)
GE_{feces} = gross energy of feces (kcal/g)
U = amount of urine collected (ml)
GE_{urine} = gross energy of urine (kcal/ml)

The following example demonstrates the use of this equation:

FI = 1,000 g
GE_{food} = 4.2 kcal/g
F = 410 g
GE_{feces} = 1.8 kcal/g
$Urine$ = 950 ml
GE_{urine} = 0.3 kcal/ml

$$\text{ME} = \frac{(1{,}000\text{ g} \times 4.2\text{ kcal/g}) - (410\text{ g} \times 1.8\text{ kcal/g}) - (950\text{ ml} \times 0.3\text{ kcal/ml})}{1{,}000\text{ g}} \times 1{,}000$$

ME = 3,180 kcal/kg

Equation B: used when urine is not collected. It is common to use standard equations for the gross energy lost in urine rather than collect urine during the experiment. Under normal physiological conditions, energy lost in urine is associated primarily with the excretion of nitrogen, and thus, it is the amount of protein in the diet that determines the gross energy of urine.

$$\text{ME (kcal/kg)} = \frac{(FI \times GE_{food}) - (F \times GE_{feces}) - [(P_{food} - P_{feces}) \times c]}{FI} \times 1{,}000$$

FI = food intake (g)
GE_{food} = gross energy of the diet/food (kcal/g)
F = amount of feces collected (g)
GE_{feces} = gross energy of feces (kcal/g)
P_{food} = amount of protein in the food (g)
P_{feces} = amount of protein in the feces (g)

c = correction factor for energy lost from protein through the excretion of urinary nitrogen. This factor is 1.25 kcal/g of protein for dogs and 0.86 kcal/g of protein for cats (AAFCO 2007).

The following example demonstrates the use of this equation:

FI = 1,000 g
GE_{food} = 4.2 kcal/g
F = 410 g
GE_{feces} = 1.8 kcal/g
P_{food} = 280g
P_{feces} = 50g
c = 1.25 kcal/g

$$\mathrm{ME} = \frac{(1{,}000\ \mathrm{g} \times 4.2\ \mathrm{kcal/g}) - (410\ \mathrm{g} \times 1.8\ \mathrm{kcal/g}) - [(280\ \mathrm{g} - 50\ \mathrm{g}) \times 1.25\ \mathrm{kcal/g}]}{1{,}000\ \mathrm{g}} \times 1{,}000$$

ME = 3,175 kcal/kg

It should be noted that by definition ME equals DE minus the GE of both urine and combustible gases. However, dogs and cats produce relatively little combustible gas from fermentation in the gastrointestinal tract. Thus, it is common practice to consider the gross energy of combustible gases as negligible in dogs and cats, and the gross energy of gases is generally ignored in experiments measuring ME.

Data from experiments that measured ME have been used to develop factors for calculating ME from diet nutrient composition. Calculating ME through the use of standard factors is the most common way of obtaining an ME value for a particular diet. It is also the fastest and easiest way to predict ME content. Although the factors used to calculate ME were derived from experiments, assumptions about GE of nutrients and nutrient digestibility had to be made to develop equations that could widely be applied to diets. To illustrate where these assumptions occur and to demonstrate how the ME equations were obtained, it is a useful exercise to work through the calculation of GE, DE, and ME for a sample diet. For this purpose, a diet with the following nutrient composition will be used:

Crude Fat = 12.0%

Crude Protein = 22.0%

Carbohydrates (nitrogen free extract) = 46.0%

Crude Fiber = 3.0%

Ash = 7.0%

Moisture = 10.0%

GE is calculated by multiplying each nutrient by a standard GE value for that nutrient. The GE values for triglycerides range from 6.5 to 9.9 kcal per gram (depending on fatty acid chain length and degree of unsaturation), proteins range from 4.0 to 8.3 kcal/g (depending on amino acid composition), and carbohydrates range from 3.7 to 4.3 kcal/g (Livesey and Elia 1988; Elia and Livesey 1992). Standard GE values of 9.4, 5.65, and 4.15 are routinely used for fats, proteins, and carbohydrates, respectively. These values are in good agreement with measured GE of pet food ingredients (Kienzle, Schrage et al. 2002). The GE of a diet can be estimated using the following equation:

$$\begin{aligned}\mathrm{GE\ (kcal/kg)} = 10[&(9.4\ \mathrm{kcal/g} \times \%\ \mathrm{crude\ fat}) \\ &+ (5.65\ \mathrm{kcal/g} \times \%\ \mathrm{crude\ protein}) + (4.15\ \mathrm{kcal/g} \\ &\times \%\ \mathrm{nitrogen\ free\ extract}) \\ &+ (4.15\ \mathrm{kcal/g} \times \%\ \mathrm{crude\ fiber})]\end{aligned}$$

Using values from the sample diet the following result is obtained:

$$\begin{aligned}\mathrm{GE\ (kcal/kg)} = 10[&(9.4\ \mathrm{kcal/g} \times 12) + (5.65\ \mathrm{kcal/g} \times 22) \\ &+ (4.15\ \mathrm{kcal/g} \times 46) + (4.15 \times 3)]\end{aligned}$$

$$\mathrm{GE\ (kcal/kg)} = 4{,}404.5$$

Neither water (moisture) nor ash is combustible in a bomb calorimeter, and thus these dietary components have a GE of 0 kcal/g, and they are not included in the equation. Also, it is assumed that crude fiber has a GE value similar to that of starch, and with the exception of lignin, the data do support the idea that the GE values of various fibers are not greatly different from starch (Kienzle, Schrage et al. 2002). The primary assumption with the use of this equation is that the GE values used are representative of the energy values of the nutrients in the diet. The values used are representative of mixed triglycerides, proteins, and carbohydrates found in conventional foods, and it is unlikely that these values will produce large errors unless the diet is high in medium chain triglycerides, monosaccharides or possibly other ingredients that deviate substantially from the standard values.

DE is calculated by multiplying the GE of each nutrient by the digestibility of the nutrient. Digestibility coefficients of 0.90 for crude fat, 0.80 for crude protein, 0.85 for carbohydrates (nitrogen free extract), and 0 for crude fiber are often used for commercial dog and cat foods. The DE of a diet can be estimated using the following equation:

$$\begin{aligned}\text{DE (kcal/kg)} = 10[&(9.4\ \text{kcal/g} \times \%\ \text{crude fat} \\ &\times \text{dig. coeff. fat}) + (5.65\ \text{kcal/g} \times \%\ \text{crude protein} \\ &\times \text{dig. coeff. protein}) + (4.15\ \text{kcal/g} \\ &\times \%\ \text{nitrogen free extract} \\ &\times \text{dig. coeff. nitrogen free extract}) + (4.15\ \text{kcal/g} \\ &\times \%\ \text{crude fiber} \times \text{dig. coeff. fiber})]\end{aligned}$$

Using values from the sample diet the following result is obtained:

$$\begin{aligned}\text{DE (kcal/kg)} &= 10[(9.4\ \text{kcal/g} \times 12 \times 0.9) \\ &\quad + (5.65\ \text{kcal/g} \times 22 \times 0.8) + (4.15\ \text{kcal/g} \times 46 \times 0.85) \\ &\quad + (4.15\ \text{kcal/g} \times 3 \times 0)] \\ \text{DE (kcal/kg)} &= 3{,}632.3\end{aligned}$$

The major assumption with the use of this equation is that the digestibility coefficients for each nutrient will truly reflect the digestibility of these nutrients in the diet. This is the primary source of error in calculating the energy content of a diet. The digestibility coefficients used in the equation were determined on commercial pet foods available in the late 1970s and early 1980s (NRC 2006), and the digestibility of some current foods on the market may differ from these values. In particular, the digestibility of crude fiber and the influence of fiber on the digestibility of other nutrients are ignored in the equation. Nonetheless, the digestibility factors used in this equation still reflect reasonably well the digestibility of many pet foods on the market (Kienzle 2002). Also, these digestibility factors form the foundation for equations that are still routinely used to predict the ME content of diets.

ME is calculated using the same equation given for DE, except the GE value for protein is corrected for the energy lost in urine with the excretion of nitrogen. Thus, if a correction factor of 1.25 kcal/g of protein is used for loss of energy in urine, then the GE value of protein becomes 4.40 kcal/g ($GE_{protein}$ = 5.65 kcal/g – 1.25 kcal/g). The corrected protein GE of 4.40 kcal/g is routinely used for both dogs and cats, even though the actual value for protein in cat foods is likely higher. The ME of a diet can be estimated using the following equation:

$$\begin{aligned}\text{ME (kcal/kg)} = 10[&(9.4\ \text{kcal/g} \times \%\ \text{crude fat} \\ &\times \text{dig. coeff. fat}) + (4.40\ \text{kcal/g} \times \%\ \text{crude protein} \\ &\times \text{dig. coeff. protein}) + (4.15\ \text{kcal/g} \\ &\times \%\ \text{nitrogen free extract} \\ &\times \text{dig. coeff. nitrogen free extract})]\end{aligned}$$

Using values from the sample diet the following result is obtained:

$$\begin{aligned}\text{ME (kcal/kg)} &= 10[(9.4\ \text{kcal/g} \times 12 \times 0.9) \\ &\quad + (4.40\ \text{kcal/g} \times 22 \times 0.8) + (4.15\ \text{kcal/g} \times 46 \times 0.85)] \\ \text{ME (kcal/kg)} &= 3{,}412.3\end{aligned}$$

The ME equation relies primarily on the same assumptions used for the DE equation. In other words, assumptions made about digestibility coefficients generally have the greatest influence on both DE and ME calculations. ME values are similar to those calculated for DE, and ME is approximately 93% of DE for dog and cat foods.

Practical Equations for Predicting the ME Content of Dog and Cat Foods

Two equations (the Atwater and modified Atwater; sometimes called the AAFCO equation) are routinely used to predict the ME values of diets for dogs and cats. These equations contain factors that include energy values corrected for digestibility and loss of energy in urine. Thus, these equations are relatively simple and involve multiplying the amount of a particular nutrient by only one factor. The Atwater equation was developed over 100 years ago to predict the energy content of human diets (Atwater 1902). The Atwater equation is still used in human nutrition, and it provides a reasonable estimate for the ME value of human foods fed to dogs (and possibly cats). The Atwater equation may also be appropriate for highly digestible commercial pet foods. Following is the Atwater equation:

$$\begin{aligned}\text{ME (kcal/kg)} = 10[&(9\ \text{kcal/g} \times \%\ \text{crude fat}) \\ &+ (4\ \text{kcal/g} \times \%\ \text{crude protein}) \\ &+ (4\ \text{kcal/g} \times \%\ \text{nitrogen free extract})]\end{aligned}$$

Using values from a diet containing 12% crude fat, 22% crude protein, and 46% nitrogen free extract, the following result can be obtained with the Atwater equation:

$$\text{ME (kcal/kg)} = 10[(9\ \text{kcal/g} \times 12) + (4\ \text{kcal/g} \times 22) + (4\ \text{kcal/g} \times 46)]$$

$$\text{ME (kcal/kg)} = 3{,}800$$

The modified Atwater equation was developed by AAFCO (AAFCO 2007) to produce an equation that would better reflect the fact that the digestibility of commercial pet foods tends to be lower than the digestibility of typical human foods. Under AAFCO regulations, the modified Atwater equation may be used to determine the ME values included on pet food labels. The modified Atwater equation is as follows:

$$\text{ME (kcal/kg)} = 10[(8.5\ \text{kcal/g} \times \%\ \text{crude fat}) + (3.5\ \text{kcal/g} \times \%\ \text{crude protein}) + (3.5\ \text{kcal/g} \times \%\ \text{nitrogen free extract})]$$

Using values from a diet containing 12% crude fat, 22% crude protein, and 46% nitrogen free extract, the following result can be obtained with the modified Atwater equation:

$$\text{ME (kcal/kg)} = 10[(8.5\ \text{kcal/g} \times 12) + (3.5\ \text{kcal/g} \times 22) + (3.5\ \text{kcal/g} \times 46)]$$

$$\text{ME (kcal/kg)} = 3{,}400$$

Both the Atwater and modified Atwater equations contain assumptions about the GE and digestibility of nutrients and, therefore, should always be viewed simply as providing an estimate of the ME value of the diet. It is best if measured or average values of nutrient composition, rather than guaranteed analysis, are used for the Atwater or modified Atwater equations. However, it is often necessary to make a quick estimate of the ME value of a diet using only the guaranteed analysis provided on a pet food label. It is important to realize that the guaranteed analysis provides only upper limits of moisture, fiber, and ash content, and lower limits of protein and fat content. Thus, the guaranteed analysis does not provide a precise measure of the absolute amount of specific nutrients in the diet. It has been reported that differences between measured nutrient composition and guaranteed analysis of pet foods result in an average underestimation of ME of 230 kcal/kg when using the modified Atwater equation (Hill, Choate et al. 2009). Thus, it is important to keep in mind that the ME value obtained using the guaranteed analysis from the pet food label will likely be at least slightly lower than the true ME value of the diet. It is also important to note when using the guaranteed analysis from pet food labels that values for ash and nitrogen free extract are not required to be listed on the label. Thus, to roughly estimate the ME content of a diet it may be necessary to calculate nitrogen free extract (NFE = 100 – % crude protein – % crude fat – % crude fiber – % moisture – % ash) by estimating the ash content of the diet. Ash values of 2.5% for canned and 8% for dried diets may be used to provide a rough estimate of NFE. However, it should be noted that there can be large variations in the ash content between different diets and use of an assumed ash value can lead to over- or underestimates of NFE.

With the development of a wide range of pet foods that differ in digestibility, there has been debate about whether the modified Atwater equation still adequately predicts the ME value of diets. It has been reported that the equation predicts the ME content of average pet foods with reasonable precision (Kienzle 2002), and the equation provides adequate estimates of the ME content of dry dog foods and canned cat foods (Laflamme 2001). The modified Atwater equation tends to underestimate the ME value of cat foods with a high ME content and overestimate the value for cat foods with a low ME content (Kienzle 2002). Thus, the Atwater equation may be more appropriate for diets with high energy values and high digestibility. There is also some question about whether the same equation should be used for dog and cat foods, since it has been shown that the digestibility of fat tends to be lower in cats than in dogs (Kendall et al. 1982). Nonetheless, it is common to use the same equations for both dog and cat foods and these equations seem to work reasonably well at providing estimates of the ME contents of many diets. The Atwater and modified Atwater equations are easy to memorize and use, and they provide quick estimates of the ME contents of diets.

Major assumptions are made about nutrient digestibility for all of the equations presented in this section. In particular, the influence of crude fiber on digestibility has been ignored. There has been interest in developing equations that use dietary crude fiber to better estimate the ME content of commercial dog and cat foods. The National Research Council (NRC) has recently recommended separate equations for dog and cat foods using crude fiber to better predict the ME content of diets (NRC 2006). The equation for dog food is:

Step 1: GE (kcal) = (5.7 × g protein) + (9.4 × g fat) + [4.1 × (g nitrogen free extract + g fiber)]

Step 2: % energy digestibility = 91.2 – (1.43 × % crude fiber in dry matter)

Step 3: DE (kcal) = GE × (% energy digestibility/100)
Step 4: ME (kcal) = DE − (1.04 × g protein)

Similarly, the equation for cat food is:

Step 1: GE (kcal) = (5.7 × g protein) + (9.4 × g fat) + [4.1 × (g nitrogen free extract + g fiber)]
Step 2: % energy digestibility = 87.9 − (0.88 × % crude fiber in dry matter)
Step 3: DE (kcal) = GE × (% energy digestibility/100)
Step 4: ME (kcal) = DE − (0.77 × g protein)

For example, the ME value for a dog food containing 12% crude fat, 22% crude protein, 46% nitrogen free extract, 3% crude fiber, 7% ash and 10% moisture may be calculated as

Step 1: GE (kcal) = (5.7 × .22) + (9.4 × .12) + [4.1 × (.46 + .03)] = 4.39
Step 2: % energy digestibility = 91.2 − (1.43 × 3.3_a) = 86.48
Step 3: DE (kcal) = 4.39 × (86.48/100) = 3.80
Step 4: ME (kcal) = 3.80 − (1.04 × .22) = 3.57

[a]Crude fiber on a dry matter basis is calculated as fiber (DM) = fiber (as fed)/(DM/100)

These equations take into consideration the influence of crude fiber on digestibility. They also take into consideration differences in digestibility and urinary energy loss between dogs and cats. These equations may be difficult to memorize or use when quickly obtaining an estimate of ME in conditions when access to references is not readily available, and these equations may not offer substantial improvement over the modified Atwater equation for average pet foods. However, these equations currently appear to do the best job predicting ME value over the wide range of pet food currently on the market. Figure 3.2 provides a summary of the methods used to estimate the metabolizable energy content of a diet.

CALCULATING ENERGY REQUIREMENT FROM BODY WEIGHT

Methods of Determining Energy Expenditure and Energy Requirements

The energy requirements of an animal can be determined by accurately measuring either energy intake or energy expenditure. These measurements are the only ways to precisely determine the energy requirement of an individual animal. Data from these measurements have been used to develop equations for predicting animal energy requirements.

As discussed in the diet records or history section of this chapter, measuring energy intake in a weight-stable animal is the best way to determine the maintenance energy requirement of the animal. A standard way, especially in growing animals, to determine maintenance energy requirements has been to feed animals over a range of energy intakes and measure change in body weight. Energy intake may then be plotted against change in body weight and regression equations can be used to fit a line or curve through the data points. The point where change in body weight equals zero is the maintenance energy requirement. In contrast to this method, studies in dogs and cats often simply measure energy intake in adult animals that are weight stable or adjust energy intake until weight stability is achieved. The maintenance energy requirement is then taken as the amount of energy consumed by the weight-stable dog or cat. The primary advantage of this method is that it does not require expensive laboratory equipment, and only balances are needed to weigh the food and animal. The major disadvantage of this method is that it can be time consuming since measurements need to be completed over a sufficient amount of time to make certain that the animal is truly weight stable.

Direct calorimetry has also been used as a method to determine energy requirements. Direct calorimetry measures heat production by the animal to determine energy expenditure and energy requirements. Direct calorimetry works because at maintenance, energy consumed is expended and released as heat (no net gain in body energy). Modern direct calorimeters consist of a chamber surrounded by temperature probes or a thermal jacket that absorbs heat. The rate of temperature change by the thermal jacket (or probe) is proportional to the heat production by the animal. This can be expressed as kcal or kJ per unit of time and equals the energy expenditure and energy requirement for the animal. These calorimetry systems can be very accurate, but the systems are expensive, and they require considerable expertise for proper use. Also, the measurements must be made in a calorimeter, and the environment in the calorimeter can be very different from normal housing conditions for the animal. Direct calorimetry also assumes no energy or heat storage in the animal and that all energy transferred from the animal occurs as heat. There are relatively few large animal direct calorimeters, and this method has not been commonly used to determine energy requirements in dogs and cats.

Indirect respiration calorimetry is a method that has frequently been used to measure energy expenditure in both dogs and cats. Indirect respiration calorimetry

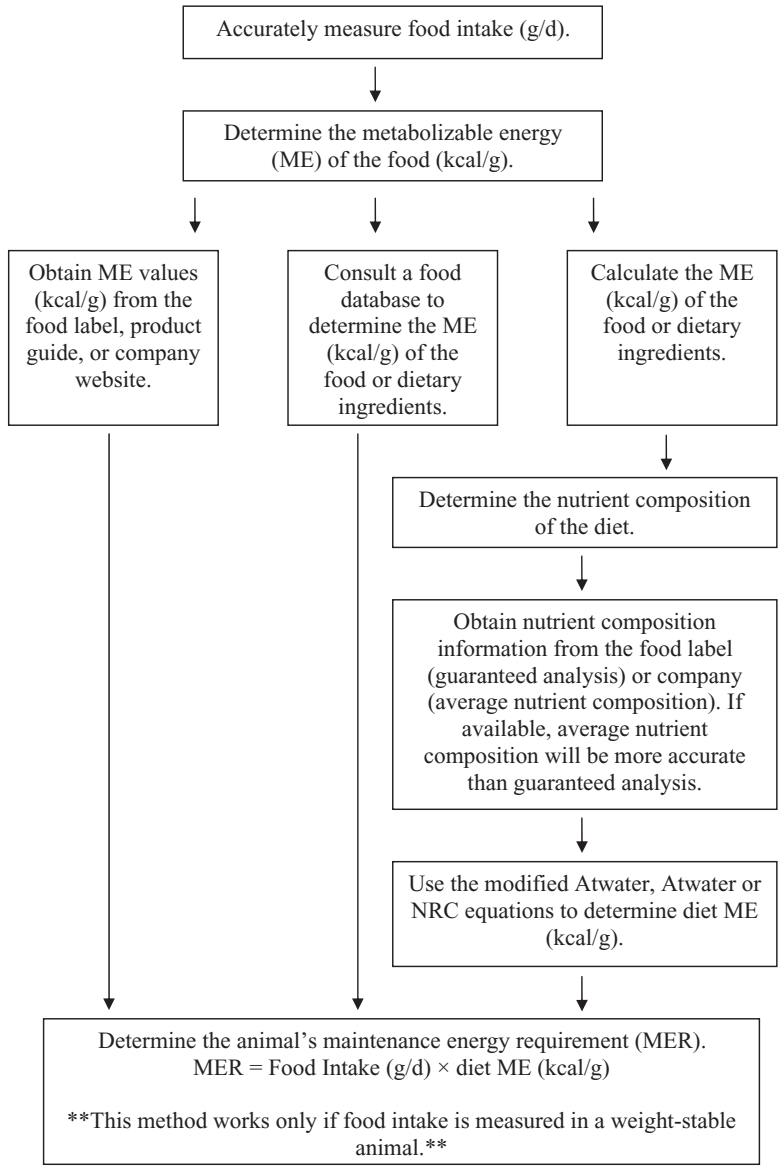

Fig. 3.2. A summary of the steps required to estimate the metabolizable energy content of a diet.

measures oxygen consumption and/or carbon dioxide production and energy expenditure is calculated from these values. Indirect respiration calorimetry works because the heat released (kcal or kJ) during the oxidation of a particle nutrient/substrate is constant. The ratio of carbon dioxide produced to oxygen consumed (CO_2/O_2) is termed the respiratory quotient, and this indicates which substrates are being oxidized and the amount of heat released per liter of oxygen consumed and liter of carbon dioxide produced.

The following values are standard numbers used for respiratory quotient and heat equivalents of oxygen and carbon dioxide (Blaxter 1989):

Lipids = 0.71 RQ, 4.71 kcal/l O_2 consumed, 6.64 kcal/l CO_2 produced

Proteins = 0.81 RQ, 4.59 kcal/l O_2 consumed, 5.69 kcal/l CO_2 produced

$$\text{Carbohydrates} = 1.0\ \text{RQ}, 5.07\ \text{kcal/l}\ O_2\ \text{consumed}, 5.07\ \text{kcal/l}\ CO_2\ \text{produced}$$

RQ ("respiratory quotient") is important not only because it provides information about the substrates being oxidized by the animal, but it can also provide information about energy expenditure. The energy expenditure (or heat production) per liter of oxygen or carbon dioxide is unique for each value of RQ. Thus, energy expenditure can be calculated from either gas if a reasonable estimate of the expected RQ of the animal can be made. Alternatively, information about the heat production associated with the oxidation of specific substrates has been used to develop equations that allow for the very accurate calculation of energy expenditure if oxygen consumption, carbon dioxide production, and urinary nitrogen can be measured. An example is the Weir equation (Weir 1949):

$$\text{Energy Expenditure (kcal)} = 3.94\,(\text{L}\ O_2) + 1.11\,(\text{L}\ CO_2) - 2.17\,(\text{g N*})$$

*N refers to grams of urinary nitrogen

Three methods are commonly used for indirect respiration calorimetry. These are the calorimetry chamber, face mask, and doubly labeled water methods. The calorimetry chamber method involves placing the animal in a sealed chamber. The rate of air flow through the chamber is carefully regulated and O_2 and CO_2 content of the inlet and outlet air is measured. Oxygen consumption and carbon dioxide production are calculated from these measures of air flow (l/min) and differences in the concentration of O_2 and CO_2 between the air entering and leaving the chamber.

The face mask method involves placing a sealed mask over the mouth and nostrils of the animal. Air flow through the mask and the gas content of the air flowing into and out of the mask is measured.

The doubly labeled water method involves administering a dose of $^2H_2{}^{18}O$ to the animal (usually as an injection). Urine or blood samples are collected at some later time to determine differences in the concentration of the two isotopes ($^2H_2$ and ^{18}O). The isotope ^{18}O may be lost from the body as either carbon dioxide or water, while $^2H_2$ is lost from the body as water only. The difference in the concentration of the two isotopes thus gives a measure of carbon dioxide production. Energy expenditure may then be calculated from this measure of carbon dioxide production using an assumed RQ.

The advantages of indirect respiration calorimetry include the fact that these methods can provide a very accurate measure of energy expenditure, and consequently energy requirements for maintenance. The measurements, at least in the case of the doubly labeled water method, can also be completed in the animal's home environment. Indirect respiration calorimetry can provide a measure of energy expenditure over a short period of time, and resting energy expenditure values can be obtained from properly adapted animals in a matter of minutes or hours. The primary disadvantage of the indirect respiration calorimetry method is that the equipment (i.e., gas analyzers, chambers, flow meters, mass spectrometer for doubly labeled water) required for these measurements is expensive and requires some expertise to operate. Thus, while indirect respiration calorimetry is widely used in laboratory settings for measuring energy expenditure and determining energy requirements, this method has not yet found widespread use in veterinary clinics and hospitals.

Methods of Calculating Energy Expenditure and Energy Requirements

Body weight is the primary component used in all equations for calculating maintenance energy requirements. Larger animals have a greater energy expenditure (kcal or kJ/day) than small animals. However, when energy expenditure is divided by body weight (kcal or KJ/kg/day), large animals have a lower energy expenditure than small animals. In other words, large animals consume less food and produce less heat per unit of mass than small animals. For example, a rat weighing 1 pound will eat 72 kcal/day. If this same energy intake were directly extrapolated to an 80-pound dog, the dog would consume 5,760 kcal per day!

The relationship between energy expenditure and body weight has been studied by many groups. In the 19th century, scientists proposed that energy expenditure was related to body surface area. Equations were developed that showed that in bodies that are geometrically similar, surface area is related to weight by the function $kg^{0.67}$ (Blanc et al. 2003; Hill and Scott 2004). Thus, small animals have a greater surface area for their body weight than large animals. Rubner (1883) proposed that energy expenditure is constant at 1,000 kcal/m^2 body surface area, and other studies have suggested that weight is related to energy expenditure by the mass exponent $kg^{0.67}$. The mass exponent $kg^{0.67}$ is still frequently used today to normalize energy expenditure for differences in body weight.

In the 1930s, Brody at the University of Missouri plotted basal energy expenditure against body weight in animals ranging in size from mice and canaries to elephants, and determined that the curve running through the data points was best represented by the following equation (kg

BW = body weight in kilograms) (Brody and Procter 1932; Brody et al. 1934):

$$\text{Basal metabolism (kcal/day)} = 70 \times \text{kg BW}^{0.734}$$

At the same time, Kleiber at the University of California Davis was also comparing basal energy expenditure and body weight data from adult animals covering a wide range of body sizes and determined that $BW^{0.75}$ fit the energy expenditure data as well as $BW^{0.73}$ (Kleiber 1961). Prior to the use of computers and scientific calculators, it was also easier to calculate $BW^{0.75}$ than $BW^{0.73}$ when using a slide rule, and the equation proposed by Kleiber has remained the standard equation for predicting basal energy expenditure in adult animals. Although Brody and Kleiber used the term "basal metabolism" with their equations, the conditions used to measure energy expenditure in the animals studied may best be described as resting energy expenditure under fasting conditions since the stringent requirements for measuring basal metabolic rate were not likely met in many of the measurements. Thus, it can be considered that Kleiber's equation predicts resting energy expenditure. The equation is:

$$\text{Resting energy expenditure (kcal/day)} = 70 \times \text{kg BW}^{0.75}$$

Resting energy requirements calculated for adult dogs and cats using this equation are provided in Tables 3.1 and 3.2, respectively.

Energy Requirements for Maintenance

It has been common to assume that resting energy expenditure is responsible for 50% of total energy expenditure in the typical adult animal. Therefore, multiplying 70 in the above equation by a factor of 2 provides the following equation to estimate maintenance energy requirements in adult animals:

$$\text{Maintenance (kcal/day)} = 140 \times \text{kg BW}^{0.75}$$

It is important to note that the exponent 0.75 used in the above equations was simply determined from the regression equation that best fit the energy expenditure and body weight data, and the physiological meaning of this exponent is still the subject of considerable debate. The 0.75 exponent was derived from comparisons across species, and this exponent may not be appropriate for some comparisons within a species.

For dogs and cats, there have generally been two approaches to calculating maintenance energy requirements. The first approach has been to calculate resting energy expenditure using Kleiber's equation ($70 \times \text{kg BW}^{0.75}$) or a linear equation such as resting energy expenditure (kcal/g) = 70 + (30 × kg BW) (Thatcher et al. 2000). The same equations for calculating maintenance energy requirements are commonly used for both dogs and cats. Maintenance energy requirements are then multiplied by a factor that takes into account the age, activity, or physiological condition of the animal. For example, the following factors have been proposed for cats: neutered adult = 1.2; intact adult = 1.4; active adult = 1.6; obese prone adult = 1.0; and dogs: neutered adult = 1.6; intact adult = 1.8; obese prone = 1.4; light work = 2; moderate work = 3; heavy work = 4–8 (Thatcher et al. 2000).

Example Calculation: What would be the predicted maintenance energy requirement for a neutered, adult cat with a body weight of 6 kg?

$$\text{ME at maintenance (kcal/day)} = 1.2 \times 70\,(6)^{0.75}$$
$$= 322 \text{ kcal/day}$$

The primary advantage of these factorial calculations is that the calculations give the veterinarian or nutritionist the flexibility to select or devise a factor that they feel will best predict the energy needs of the animal. However, the disadvantages of the factorial approach are that it is often unclear how the factors were derived and that the factors have not been rigorously tested to determine if they predict energy requirements better than other equations. Also, the large number of factors can sometimes make it difficult to determine which factor is most appropriate for an individual animal.

The second approach has been to use an equation that was developed specifically to predict maintenance energy requirements. Maintenance energy requirements calculated for adult dogs and cats using this approach are provided in Tables 3.1 and 3.2, respectively. The NRC uses the following equation to predict maintenance energy requirement for kennel dogs or active pet dogs (NRC 2006):

$$\text{ME at maintenance} = 130 \text{ kg} \times \text{BW}^{0.75} \text{ kcal/day}$$

Equations using different multipliers are recommended for groups of dogs that have been reported to have higher or lower energy requirements than those obtained from the standard maintenance energy requirement equation. Rather than use 130 in the above equation, it is recommended that following multipliers are used for the indicated groups of dogs (NRC 2006):

Table 3.1. Resting and Maintenance Energy Requirements (kcal/day) of Adult Dogs

Body Weight (kg)	Body Weight (lbs)	RER[a]	MER[b] active pet dogs	MER[c] young dogs	MER[d] inactive dogs	MER[e] active old dogs
1	2.2	70	130	140	95	105
2	4.4	118	219	235	160	177
3	6.6	160	296	319	217	239
4	8.8	198	368	396	269	297
5	11	234	435	468	318	351
6	13.2	268	498	537	364	403
7	15.4	301	559	602	409	452
8	17.6	333	618	666	452	499
9	19.8	364	675	727	494	546
10	22	394	731	787	534	590
11	24.2	423	785	846	574	634
12	26.4	451	838	903	613	677
13	28.6	479	890	958	650	719
14	30.8	507	941	1013	688	760
15	33	534	991	1067	724	800
16	35.2	560	1040	1120	760	840
17	37.4	586	1088	1172	795	879
18	39.6	612	1136	1223	830	918
19	41.8	637	1183	1274	865	956
20	44	662	1229	1324	898	993
21	46.2	687	1275	1373	932	1030
22	48.4	711	1321	1422	965	1067
23	50.6	735	1365	1470	998	1103
24	52.8	759	1410	1518	1030	1139
25	55	783	1453	1565	1062	1174
26	57.2	806	1497	1612	1094	1209
27	59.4	829	1540	1658	1125	1244
28	61.6	852	1582	1704	1156	1278
29	63.8	875	1625	1750	1187	1312
30	66	897	1666	1795	1218	1346
31	68.2	920	1708	1839	1248	1379
32	70.4	942	1749	1884	1278	1413
33	72.6	964	1790	1928	1308	1446
34	74.8	986	1830	1971	1338	1478
35	77	1007	1871	2015	1367	1511
36	79.2	1029	1911	2058	1396	1543
37	81.4	1050	1950	2100	1425	1575
38	83.6	1071	1990	2143	1454	1607
39	85.8	1092	2029	2185	1483	1639
40	88	1113	2068	2227	1511	1670
41	90.2	1134	2106	2268	1539	1701
42	92.4	1155	2145	2310	1567	1732
43	94.6	1175	2183	2351	1595	1763
44	96.8	1196	2221	2392	1623	1794
45	99	1216	2259	2432	1651	1824

Continued

Table 3.1. *Continued*

Body Weight (kg)	Body Weight (lbs)	RER[a]	MER[b] active pet dogs	MER[c] young dogs	MER[d] inactive dogs	MER[e] active old dogs
46	101.2	1236	2296	2473	1678	1855
47	103.4	1257	2334	2513	1705	1885
48	105.6	1277	2371	2553	1732	1915
49	107.8	1296	2408	2593	1759	1945
50	110	1316	2444	2632	1786	1974
51	112.2	1336	2481	2672	1813	2004
52	114.4	1356	2517	2711	1840	2033
53	116.6	1375	2554	2750	1866	2063
54	118.8	1394	2590	2789	1892	2092
55	121	1414	2626	2827	1919	2121
56	123.2	1433	2661	2866	1945	2149
57	125.4	1452	2697	2904	1971	2178
58	127.6	1471	2732	2942	1997	2207
59	129.8	1490	2767	2980	2022	2235
60	132	1509	2803	3018	2048	2264
61	134.2	1528	2838	3056	2074	2292
62	136.4	1547	2872	3093	2099	2320
63	138.6	1565	2907	3131	2124	2348
64	140.8	1584	2942	3168	2150	2376
65	143	1602	2976	3205	2175	2404
66	145.2	1621	3010	3242	2200	2431
67	147.4	1639	3044	3279	2225	2459
68	149.6	1658	3078	3315	2250	2486
69	151.8	1676	3112	3352	2274	2514
70	154	1694	3146	3388	2299	2541
71	156.2	1712	3180	3424	2324	2568
72	158.4	1730	3213	3460	2348	2595
73	160.6	1748	3247	3496	2373	2622
74	162.8	1766	3280	3532	2397	2649
75	165	1784	3313	3568	2421	2676
76	167.2	1802	3346	3604	2445	2703
77	169.4	1820	3379	3639	2469	2729
78	171.6	1837	3412	3675	2493	2756
79	173.8	1855	3445	3710	2517	2782
80	176	1872	3477	3745	2541	2809

[a]RER = resting energy requirement = $70 \times \text{kg BW}^{0.75}$.
[b]MER = maintenance energy requirement for active pet dogs or kennel dogs = $130 \times \text{kg BW}^{0.75}$.
[c]MER = maintenance energy requirement for active young adult dogs = $140 \times \text{kg BW}^{0.75}$.
[d]MER = maintenance energy requirement for inactive dogs = $95 \times \text{kg BW}^{0.75}$.
[e]MER = maintenance energy requirement for older active dogs e = $105 \times \text{kg BW}^{0.75}$.

Dog Group	Multiplier
Young, active dogs	140 (ex. ME_m = 140 kg $BW^{0.75}$)
Active Great Danes	200
Active Terriers	180
Inactive dogs	95
Newfoundlands	105
Older active dogs	105

Example Calculation: What would be the predicted maintenance energy requirement for an active mixed breed dog with a body weight of 30 kg?

$$\text{ME at maintenance (kcal/day)} = 130 \times (30\text{ kg})^{0.75}$$
$$= 1{,}666\text{ kcal/day}$$

In some cases, there is an advantage to having an equation that can easily be calculated without using exponents of body weight. The following linear equation is provided by the NRC and gives results comparable to the equation using $W^{0.75}$ for dogs weighing 8 to 20 kg (NRC 2006):

$$\text{ME at maintenance} = 358 + (39 \times \text{kg BW})$$

The NRC equations for predicting maintenance energy requirements in cats are as follows (NRC 2006):

Lean Domestic Cats[a]:

$$\text{ME at maintenance (kcal/day)} = 100\text{ kg BW}^{0.67}$$

Overweight Cats[b]:

$$\text{ME at maintenance (kcal/day)} = 130\text{ kg BW}^{0.40}$$

[a]"Lean" refers to cats with a body condition score of less than or equal to 5 on a 9-point scale.
[b]"Overweight" refers to cats with a body condition score of greater than or equal to 6 on a 9-point scale.

Example Calculation: What would be the predicted maintenance energy requirement for a 4-kg lean cat?

$$\text{MEm (kcal/day)} = 100 \times (4\text{ kg})^{0.67} = 253\text{ kcal/day}$$

A linear equation was used to calculate maintenance energy requirements for cats in the 1986 NRC. This equation overestimated the energy requirements for large cats and led to the recent development of equations for lean and overweight cats. Nonetheless, the linear equation may still be useful for a quick estimate of energy requirements, without the need to calculate exponents of body weight. The cat linear equations are (NRC 1986):

Active Cats:

$$\text{ME at maintenance (kcal/day)} = 80 \times \text{kg BW}$$

Inactive Cats:

$$\text{ME at maintenance (kcal/day)} = 70 \times \text{kg BW}$$

Figure 3.3 shows a comparison of maintenance energy requirements calculated using either an exponential or linear equation. The steps for calculating maintenance energy requirements for both dogs and cats are summarized in Fig. 3.4.

Table 3.2. Resting and Maintenance Energy Requirements (kcal/day) of Adult Cats

Body Weight (kg)	Body Weight (lb)	RER[a]	MER[b] lean cats	MER[c] overweight cats
1	2.2	70	100	130
1.5	3.3	95	131	153
2	4.4	118	159	172
2.5	5.5	139	185	188
3	6.6	160	209	202
3.5	7.7	179	231	215
4	8.8	198	253	226
4.5	9.9	216	274	237
5	11	234	294	247
5.5	12.1	251	313	257
6	13.2	268	332	266
6.5	14.3	285	350	275
7	15.4	301	368	283
7.5	16.5	317	386	291
8	17.6	333	403	299
8.5	18.7	348	419	306
9	19.8	364	436	313
9.5	20.9	379	452	320
10	22	394	468	327

[a]RER = resting energy requirement = 70 × kg $BW^{0.75}$
[b]MER = maintenance energy requirement for lean cats = 100 × kg $BW^{0.67}$
[c]MER = maintenance energy requirement for obese cats = 130 × kg $BW^{0.40}$

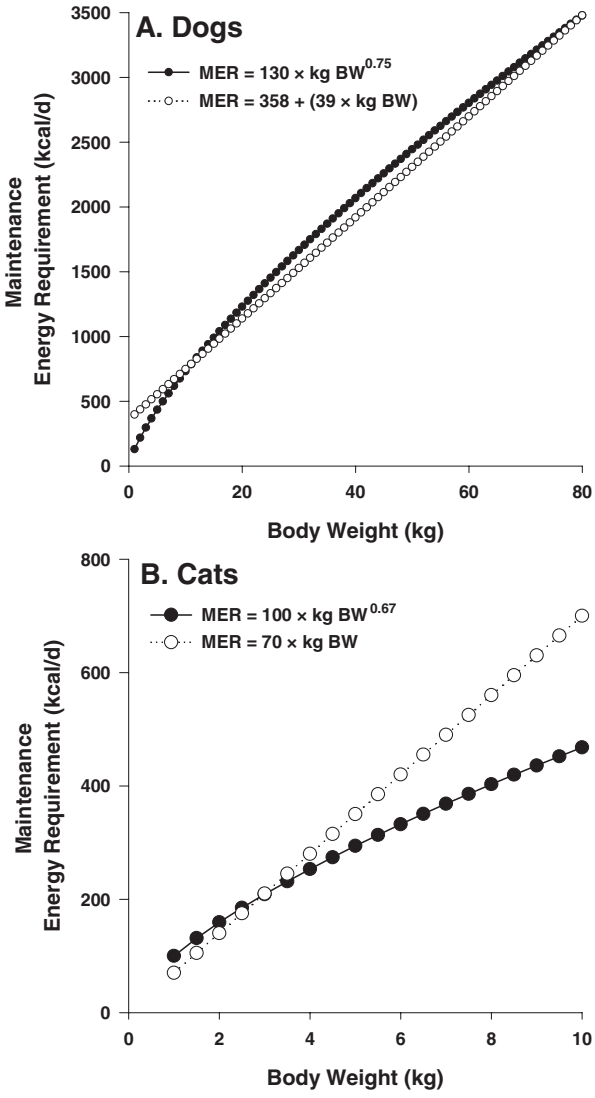

Fig. 3.3. Comparisons of maintenance energy requirements for dogs (panel A) and cats (panel B) using linear or exponential equations.

It is important to note that prediction equations provide only a rough estimate of energy requirements for individual animals (they predict the requirements for the "average" animal). There is considerable variation in energy requirements between animals, and the true energy requirements of an individual animal may differ by as much as 50% from predicted values. Therefore, the equations simply provide a starting point for determining how much to feed an animal. Energy intake would clearly need to be adjusted if the predicted maintenance energy requirements caused either an increase or decrease in body weight. The best equation to use for predicting the maintenance energy requirement of an individual animal is somewhat of an academic argument since none of the equations account for the tremendous amount of individual variability that is observed in the energy requirements of dogs and cats. The equations simply allow the user to take an educated guess at the maintenance energy requirements of a particular animal. It is important for a veterinarian or nutritionist to tell clients that it is not currently possible to precisely predict the energy requirement of an individual animal and that energy calculations simply provide a starting point for determining the correct amount to feed the animal. It should be clear that adjustments in energy intake may be required to find the animal's true maintenance energy requirement.

Energy Requirements for Growth

The requirement for energy increases during growth. During this process, some energy is deposited in tissue, and some energy is expended in the process of building new tissue:

Energy Intake → Maintenance Energy Expenditure
+ Energy Expenditure Associated with Tissue Synthesis
+ Energy Deposited in Tissue

Efficiency of energy use in maintenance and growth differs because the energy costs of anabolic and catabolic pathways differ. In general, efficiency of energy use in growth is low. Therefore, on a per-unit weight basis, the energy requirement for growth is greater than that for maintenance.

Growing puppies require approximately two times as much energy per gram of body weight as adult dogs (Arnold and Elvehjem 1939). However, energy requirements change as a dog grows from weaning to adult body weight. Predicted energy requirements are approximately 2.5 times maintenance requirements at weaning and requirements decrease to approximately 1.5 times maintenance requirements by the time the dog reaches 60% of maximal mature weight. A factorial approach may be used to calculate energy requirements for growth by multiplying formulas for predicting maintenance energy requirements by these factors. The energy requirements for growth in dogs can be predicted using the following equation (NRC 2006):

$$\text{ME (kcal/day)} = 130 \times \text{BW}_c^{0.75} \times [3.2 \times (e^{-0.87p} - 0.1)],$$

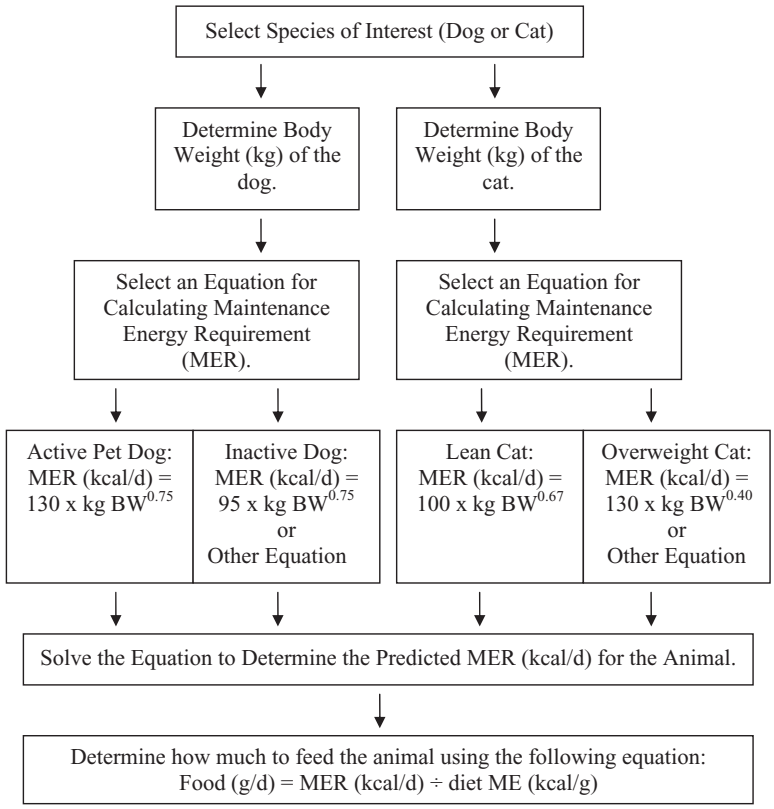

Fig. 3.4. A summary of the steps required to estimate the maintenance energy requirements for dogs or cats.

where:
BWc = current body weight in kg
e = base of natural log (i.e., 2.71828...)
p = current body weight divided by expected mature body weight

Notice that the first part of the equation ($130 \times BW_c^{0.75}$) simply calculates maintenance energy requirements. All animals have a maintenance energy requirement, and energy required for growth, reproduction, or other physiological processes occurs in addition to this maintenance requirement. The second part of the equation $[3.2 \times (e^{-0.87p} - 0.1)]$ includes the energy required for growth.

Example Calculation: What is the daily energy requirement for a 3-month-old Golden Retriever puppy that weighs 11 kg and has an expected mature body weight of 30 kg?

$$\begin{aligned} \text{ME (kcal/day)} &= 130 \times 11\,\text{kg}^{0.75} \times 3.2 \times [e^{-0.87(11/30)} - 0.1] \\ &= 130 \times 6.04 \times 3.2 \times [e^{-0.319} - 0.1] \\ &= 2512.64 \times .627 \\ &= 1{,}575\ \text{kcal/day} \end{aligned}$$

For dogs, the equations for predicting energy requirements for growth should simply serve as a starting point for determining how much to feed puppies. Puppies should always be fed to promote optimal growth rather than maximal growth. Optimal growth requires monitoring body condition score and adjusting energy intake as needed. For purebred dogs, puppy weights should be compared to growth standards for the breed and energy intake should be adjusted if the puppies deviate from these standards. It has been shown that Newfoundland puppies require less energy (kcal/kg body weight) than Great Dane puppies, despite the fact that they grow at the same rate

(Legrand-Defretin 1994). Labrador puppies also appear to require less energy (kcal/kg body weight) than Briard puppies (Legrand-Defretin 1994), and this further supports the point that purebred puppies should be fed to support the appropriate growth rate for their breed and to maintain an ideal body condition score.

Similar to dogs, a detailed equation has been developed to predict the energy requirements for growth in kittens (NRC 2006):

$$\text{ME (kcal/day)} = 100 \times \text{BW}_c^{0.67} \times 6.7 \times [e^{-0.189p} - 0.66], \text{ where:}$$

BW_c = current body weight in kg
e = base of natural log (i.e., 2.71828...)
p = current body weight divided by expected mature body weight.

To allow kittens to meet their energy requirements, it is generally recommended that they be provided with *ad libitum* access to food. The NRC equation provides an estimate of the expected energy intake of kittens and provides a quantitative way to see how energy requirements change as an animal approaches adult body weight.

Energy Requirements for Pregnancy and Lactation

Similar to growth, the energy requirements during both pregnancy and lactation are greater than maintenance because of the energetic cost of fetal growth or milk production. In bitches, no increase in energy intake is required until 4 to 5 weeks after mating (Case et al. 2000; NRC 2006). At this time, and until parturition, energy requirements will increase by 25% to over 60% depending on the size of the bitch (the percent increase in energy requirements during pregnancy tends to be greater for large breed bitches). The following equation is used to predict energy requirements in bitches during late gestation (NRC 2006):

$$\text{ME (kcal/day)} = 130 \times \text{kg BW}^{0.75} + (26 \times \text{kg BW})$$

Notice that the first part of the equation ($130 \times \text{kg BW}^{0.75}$) is simply the maintenance energy requirement of the bitch, and the second part of the equation (26 + kg BW) is the energy required for weight gain during gestation.

Queens should be fed to encourage a 40–50% increase in body weight during pregnancy (Loveridge 1986). In general, energy requirements for queens increase by approximately 40% during pregnancy. The following equation has been used to predict energy requirements in queens during pregnancy (NRC 2006):

$$\text{ME (kcal/day)} = 140 \times \text{kg BW}^{0.67}$$

However, it is common practice to allow queens *ad libitum* access to food during pregnancy to promote weight gain, which is needed to subsequently support lactation.

Lactation represents the greatest energy demand on the animal. It can often be difficult for the female to consume enough energy to meet this great demand, and thus it is common practice to allow bitches and queens *ad libitum* access to food through at least the first several weeks of lactation. The energy cost of lactation will vary depending on the number of offspring, and the amount of solid food that is given to the offspring. Puppies and kittens are often weaned by 8 weeks of age, and solid food should be offered to the puppies and kittens by 3 to 4 weeks of age (Case et al. 2000). Energy requirements are typically increased by two to four times maintenance requirements during lactation in bitches or queens. Energy requirements during lactation in bitches may be calculated using the following equation (NRC 2006):

$$\text{ME (kcal/day)} = 145 \times \text{kg BW}^{0.75} + [\text{kg BW} (24n + 12m) \times L],$$

where:
kg BW = body weight of the dog in kg
n = number of puppies between 1 and 4
m = number of puppies between 5 and 8
L = correction factor for stage of lactation (week 1 = 0.75, week 2 = 0.95, week 3 = 1.1, week 4 = 1.2)

Example calculation: What is the daily energy requirement of a 35-kg Labrador Retriever in the second week of lactation nursing five puppies?

$$\text{ME (kcal/day)} = 145 \times 35^{0.75} + 35[(24 \times 4) + (12 \times 1)] \times 0.95$$

$$\text{ME (kcal/day)} = 2086.5 + 35(96 + 12) \times 0.95$$

$$\text{ME (kcal/day)} = 2086.5 + 3780 \times 0.95$$
$$= 2086.5 + 3591$$
$$= 5{,}678 \text{ kcal/day}$$

Energy requirements during lactation in cats may be calculated using the following equations (NRC 2006):

Fewer than three kittens:

$$\text{ME (kcal/day)} = 100 \times \text{kg BW}^{0.67} + (18 \times \text{BW kg} \times L)$$

Three to four kittens:

$$\text{ME (kcal/day)} = 100 \times \text{kg BW}^{0.67} + (60 \times \text{BW kg} \times \text{L})$$

More than four kittens:

$$\text{ME (kcal/day)} = 100 \times \text{kg BW}^{0.67} + (70 \times \text{BW kg} \times \text{L}),$$

where:
kg BW or BW kg = body weight of the cat in kg
L = correction factor for stage of lactation (week 1 = 0.9, week 2 = 0.9, week 3 = 1.2, week 4 = 1.2, week 5 = 1.1, week 6 = 1.0, week 7 = 0.8)

CALCULATING ENERGY REQUIREMENTS IN STATES OF DISEASE

It can be a challenge to determine the energy requirements of injured or ill animals. However, the proper energy intake is essential for recovery or to stabilize the illness. Energy intakes that are too low can lead to accelerated loss of lean tissue mass, which could induce further complications. In contrast, energy intakes that are too high can lead to hyperglycemia, hyperlipidemia, and hyperammonemia (Burkholder 1995). High energy intakes may also cause hepatomegaly and hyberbilirubinemia (Lowry and Brennan 1979), which may prevent proper recovery from the injury or illness. Therefore, it is important to provide an appropriate amount of dietary energy to promote recovery and prevent the development of further complications.

Unfortunately, there have been relatively few studies that have measured energy expenditure in dogs and cats with injury or illness. Some studies have used indirect respiration calorimetry using a face mask system to measure energy in dogs with osteosarcoma (Mazzaferro et al. 2001), lymphoma (Oglivie, Fettman et al. 1993), non-hematological tumors (Oglivie, Walters et al. 1996), surgery (O'Toole, Miller et al. 2004), or trauma (O'Toole, Miller et al. 2004). However, there are two key limitations with these studies. First, the face mask system of indirect respiration calorimetry requires training to ensure that the animal does not become stressed by wearing the face mask. It is only possible to obtain reliable data in well-adapted animals. One study, which completed indirect respiration calorimetry measurements over a 16-minute period repeated four times during the day, found that the most reliable measures of energy expenditure using the face mask system were obtained without the first two measurements of the day (O'Toole, McDonnell et al. 2001). This at least suggests that adaptation to the face mask was occurring with repeated measurements. In hospitalized patients, it may be difficult to adequately adapt the animals to the face mask. Second, the indirect respiration calorimetry measurements using the face mask system are completed only in animals at rest and thus provide information only about the influence of injury or illness on resting energy expenditure. The influence of injury and illness on total energy expenditure will determine the animal's energy requirement, and measures of only resting energy expenditure do not provide information about physical activity or total energy expenditure. Currently there is very limited information about the energy expenditure and energy requirements of sick or injured dogs and cats.

Because of the limited information on energy requirements in companion animals with disease, it has been necessary to use human data to devise equations for estimating energy requirements in hospitalized dogs and cats. Early studies investigating the influence of disease on energy requirements in humans often measured resting energy expenditure in patients during periods of peak hypermetabolism and then used this data to calculate energy requirements (Weekes 2007). It was often assumed that the increase in measured resting energy expenditure would translate into increases in total energy expenditure. Equations were then developed that predicted injury and illness would cause increases in energy requirements above those of a healthy animal at maintenance. Human equations were adopted for use in veterinary medicine with factors that predicted increases in maintenance energy requirements of up to twofold, depending on the injury (Donoghue 1989). However, it is now viewed that injury and illness do not generally increase overall maintenance energy requirements and often may actually decrease it. In particular, there is relatively little information about the influence of many diseases on physical activity-related energy expenditure (Kulstad and Schoeller 2007), despite the fact that this is a major contributor to maintenance energy requirements. The use of the doubly labeled water method combined with measures of resting energy expenditure, however, has allowed physical activity to be measured in human patients with diseases. Data from these studies indicate that most chronic and acute diseases produce a considerable decrease in physical activity-related energy expenditure (Elia 2005). While resting energy expenditure is often increased with acute disease (Elia 2005) and injury (Frankenfield 2006), the decrease in physical activity-related energy expenditure may negate the changes in resting energy expenditure and produce a net decrease in total energy expenditure (and maintenance

energy requirements). Decreases in total energy expenditure may also be exacerbated by medications such as sedatives and analgesics, which may make the animal drowsy and limit voluntary physical activity. Cage confinement can also limit movement and contribute to decreases in energy expenditure.

Based on current information (mostly from human studies), it is prudent to be conservative in predicting the energy requirements for dogs and cats with disease or injury. The animals should at least be fed 1.1 times resting energy expenditure to cover basal energy requirements and the thermic effect of feeding. It should rarely be necessary to feed injured or ill cats and dogs above the predicted energy requirement for a healthy animal at maintenance. A series of factors for calculating energy requirements with disease and injury have been developed for use in hospitalized human patients. These factors are multiplied by resting energy requirements to determine the energy requirements for individuals with disease or injury. Energy requirements are generally equal to 1.1–1.8 times resting energy expenditure, depending on the disease or severity of injury (Barndregt and Soeters 2005; Newton and Heimburger 2006). The following equations have been proposed for predicting energy requirements in injured or ill dog and cats (Remillard and Thatcher 1989) or humans (Lagua and Claudio 2004):

Surgery:
$$\text{ME (kcal/day)} = 1.1\text{–}1.3 \times (70 \text{ kg BW}^{0.75})$$

Cancer:
$$\text{ME (kcal/day)} = 1.2\text{–}1.5 \times (70 \text{ kg BW}^{0.75})$$

Trauma:
$$\text{ME (kcal/day)} = 1.3\text{–}1.4 \times (70 \text{ kg BW}^{0.75})$$

Multiple trauma, head trauma:
$$\text{ME (kcal/day)} = 1.5\text{–}2.3 \times (70 \text{ kg BW}^{0.75})$$

Sepsis:
$$\text{ME (kcal/day)} = 1.8\text{–}2.0 \times (70 \text{ kg BW}^{0.75})$$

Burns, <40% of body:
$$\text{ME (kcal/day)} = 1.2\text{–}1.8 \times (70 \text{ kg BW}^{0.75})$$

Burns, >40% of body:
$$\text{ME (kcal/day)} = 1.8\text{–}2.0 \times (70 \text{ kg BW}^{0.75})$$

Respiratory/renal failure:
$$\text{ME (kcal/day)} = 1.2\text{–}1.4 \times (70 \text{ kg BW}^{0.75})$$

Fractures, long bone or multiple:
$$\text{ME (kcal/day)} = 1.2\text{–}1.3 \times (70 \text{ kg BW}^{0.75})$$

Infections, mild to moderate:
$$\text{ME (kcal/day)} = 1.1\text{–}1.4 \times (70 \text{ kg BW}^{0.75})$$

Infections, severe:
$$\text{ME (kcal/day)} = 1.5\text{–}1.7 \times (70 \text{ kg BW}^{0.75})$$

These factors have not been extensively tested in dogs and cats, and use of these equations assumes that dogs and cats will have similar energetic responses to disease and injury as humans. Without additional information on changes in total energy expenditure in response to illness and injury in companion animals, it seems reasonable to target energy requirements for most sick or injured dogs and cats somewhere between resting and maintenance energy requirements. Similar to other prediction equations, the equations for predicting energy requirements of dogs and cats with disease or injury should be viewed as a starting point for determining energy requirements. Veterinarians or nutritionists should be ready to make adjustments in the energy given to the animal based on the response of the patient. A summary of the steps involved in determining how much to feed an injured or ill animal is provided in Fig. 3.5.

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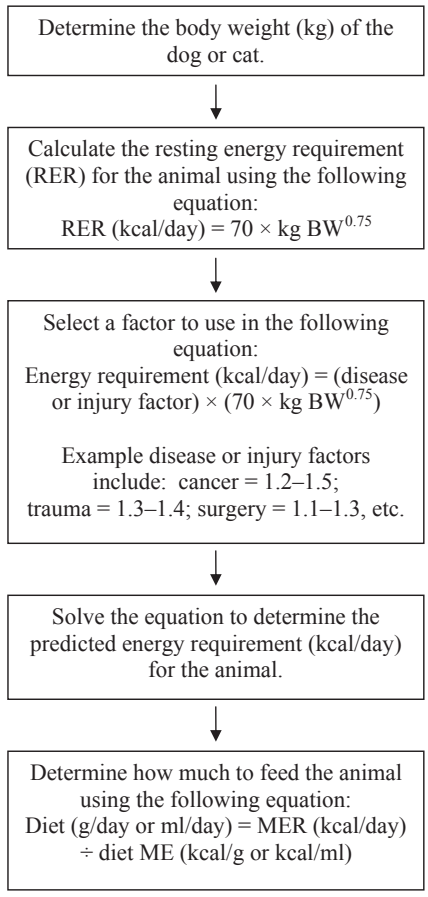

Fig. 3.5. A summary of the steps required to determine how much to feed a dog or cat that has an injury or illness.

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SUMMARY

- An accurate diet record is the best way to determine the maintenance energy requirement of an animal that is weight stable.
- The energy requirements of dogs and cats are given in units (kcal or kJ) of metabolizable energy (ME).
- The energy content of a diet may be calculated using factors that contain assumptions about the gross energy and digestibility of the diet components. The modified Atwater equation (crude protein = 3.5 kcal/g; crude fat = 8.5 kcal/g; nitrogen free extract/carbohydrate = 3.5 kcal/g) is commonly used in dog and cat nutrition, although this equation may underestimate the ME content of high-energy diets and overestimate the ME content of low-digestible, high-fiber diets.
- The resting energy requirement (RER) of dogs, cats, and other mammals may be predicted using the equation RER (kcal/day) = 70 × kg $BW^{0.75}$.
- The maintenance energy requirement (MER) of dogs and cats can be predicted using one of several equations derived specifically for determining MER or by multiplying RER by factors for activity, age, or physiological status of the animal. Because of the large variation in MER between animals, prediction equations can only provide a rough estimate of the MER for an individual animal. It is important to realize that these equations provide a starting point for determining how much to feed an animal and adjustments in energy intake may be needed to find the animal's true MER.
- Growth, pregnancy, and lactation all cause increases in energy requirements above maintenance. Increases of more than double MER occur during early growth and lactation.
- Injury and illness often cause an increase in RER but a decrease in physical activity-related energy expenditure. Overall, total energy expenditure is often not changed, or even decreased, with injury and disease. The energy requirements of hospitalized animals are often predicted by multiplying RER by a factor which adjusts for the specific disease or injury. In general, most animals with injury or disease are fed somewhere between the RER and the MER of healthy animals.

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Nutritional and Energy Requirements for Performance

4

Richard C. Hill

INTRODUCTION

The purpose of this chapter is to provide practical advice regarding the feeding of dogs that undertake different types of exercise. This advice is based on the review of the effect of physical exercise and climate on the nutrition of dogs and cats published by the National Research Council (NRC 2006). The reader should turn to that review for a more detailed explanation of the recommendations in this chapter and for the references on which they are based.

HOW MUCH TO FEED EXERCISING DOGS?

It is not possible to make an accurate recommendation of how much to feed an individual exercising dog. Theoretically, it should be possible to divide the daily metabolizable energy (ME) requirement in kcal/day by the ME density of the diet in kcal/gram to obtain the amount to feed in grams/day. Nevertheless, individual variation about the mean has always proved to be substantial when energy utilization has been measured in groups of dogs of similar body weight (BW) undertaking similar amounts of exercise. Thus, any calculation of the ME requirements based on mean energy requirements can provide no more than an uncertain estimate of the true requirements of any individual animal. It is best, therefore, not to rely on a calculation to determine how much to feed an exercising dog but instead to adjust the amount fed to ensure that the dog maintains an ideal body condition.

The ideal body condition for exercising dogs has not been determined but some studies suggest that dogs live longer and perform better when they are fed less food and consequently weigh slightly less than they would if they were given free access to food. For example, Labrador Retrievers that undertook modest amounts of activity in kennels with runs died a median of 2 years earlier and required treatment for arthritis a median of 3 years earlier when fed free choice compared to paired Retrievers fed 25% less (Kealy et al. 2002). The dogs fed less food were lean, with a mean body condition score (BCS) of 4.6 on a 9-point scale, whereas control dogs were only modestly overweight, with a mean BCS of 6.7 on the same scale. In a second study, trained Greyhounds racing over a distance of 500 m ran on average 0.7 km/h faster when weighing 6% less and being fed 15% less food than when they were fed free choice (Hill, Lewis, Randell et al. 2005). These trained racing Greyhounds had a median BCS (3.75 on a 9-point scale) when fed free choice but were leaner, with a median BCS of 3.5, when fed 15% less food.

Being overweight also has disadvantages for dogs running longer distances. When body weight increased 20% and fat mass increased from 17% to 20% in Beagles, water loss increased 50% during a 50-min run on a treadmill at 6 km/h (Young 1960). The respiratory quotient (RQ) also increased from 0.85 to 0.97 during a run when these dogs became overweight suggesting that more energy was derived from carbohydrate and less from fat. Increased use of glucose may limit stamina. Conversely, slight weight loss associated with 5 days of food deprivation increased endurance in Beagles running on a treadmill (Young 1959).

Thus, for optimum performance and long-term health, exercising dogs should not be fed free choice. An initial

Applied Veterinary Clinical Nutrition, First Edition. Edited by Andrea J. Fascetti, Sean J. Delaney.

Table 4.1. Approximate Daily Metabolizable Energy (ME) Requirements of Exercising Dogs Expressed Relative to Metabolic Body Weight[1] and "Resting Energy Expenditure (REE)"[2]

	Daily ME requirement[3]		Amount required by 25–kg dog	
Activity	kcal ME/kg $BW^{0.75}$	Ratio to REE	kcal ME	g[4]
Basal metabolic rate	76 (48–114)	1.1 (0.7–1.6)	850 (540–1,280)	190 (120–280)
Resting fed metabolic rate[5]	84 (53–125)	1.2 (0.8–1.8)	935 (590–1,410)	210 (130–310)
Pet dogs (depends on activity, breed, etc.)	(50–200)	(0.7–3)	(560–2,240)	(120–500)
Laboratory dogs in kennels with runs	130 (80–170)	1.9 (1.1–2.4)	1,450 (890–1,900)	320 (200–420)
Racing Greyhounds	140 (120–160)	2 (1.7–2.3)	1,560 (1340–1,790)	350 (300–400)
Hunting dogs	240 (200–280)	3.4 (3–4)	2,680 (2240–3,130)	600 (500–700)
Sled dogs racing long distances in the cold	1050 (860–1240)	15 (12–18)	11,700 (9,600–13,900)	2,600 (2,100–3,100)

[1]Metabolic body weight = (BW in kg) $^{0.75}$ where BW = body weight.
[2]Resting energy expenditure in kcal calculated as 70 × (body weight in kg)$^{0.75}$ or using an approximation of 30 + 70 × (body weight in kg) for medium–sized dogs. REE calculated in this way is less than the value obtained by averaging reported values for basal metabolic rate in dogs shown in the table.
[3]Values are means with ranges in parentheses.
[4]Assumes a high–fat dry diet containing 4.5 kcal/g as fed.
[5]Resting fed metabolic rate is the energy required by dogs confined to a cage and includes an additional 10% energy for assimilation of food above basal metabolic rate.

estimate of how much to feed can be obtained from the mean ME requirements of dogs undertaking different amounts exercise (Table 4.1). The amount should then be adjusted to ensure that dogs maintain a lean body condition for that breed, i.e., a BCS of 4–5 on a 9-point scale for most breeds, and a BCS of 3.5 on the same scale for Greyhounds and other sight hounds.

ENERGY REQUIREMENTS FOR PERFORMANCE AND WORK

There is a misconception among the general public that a dog such as a Greyhound that runs fast requires more energy than a dog that runs more slowly. On the contrary, whereas energy is expended more rapidly when a dog runs more rapidly, it is expended for a shorter period of time. The total energy expended relative to distance traveled does not change with speed of running because dogs, like other animals, adjust their gait to minimize energy expenditure (Blaxter 1989).

For a greater appreciation of this concept, it is necessary to consider the various parts of the energy budget for exercise. When a dog is lying down awake having not eaten for a while in a thermoneutral environment (in which it does not have to expend energy to keep itself warm), the dog expends energy to maintain itself. This basal energy (76 kcal/kg $BW^{0.75}$ daily or 13 kcal/kg $BW^{0.75}$ hourly for an average dog) (NRC 2006) is also required to maintain basic body functions during exercise. In addition, energy expenditure increases 50% when an animal stands. This energy continues to be expended all the time the dog stands for exercise irrespective of the speed of travel. Energy is expended to support horizontal motion but this energy expenditure for horizontal movement is proportional to distance traveled (approximately 1 kcal/kg BW for each horizontal kilometer traveled for a dog of more than 10 kg BW and 1.5 kcal/kg BW for each horizontal kilometer traveled for a dog of less than 10 kg) (NRC 2006).

Thus, an average 30-kg dog with a basal metabolic rate of 41 kcal/h (970 kcal daily) will require an additional 20 kcal/h when it stands and another 90 kcal if it runs slowly at 3 km/h for 3 km. Surprisingly, however, an average 30-kg dog that stands and runs at 6 km/h over those 3 km and completes the distance in half the time but then lies down for the remaining half hour would require less energy overall. The faster animal remains standing for only half the time and so uses less energy for standing (only 10 kcal), whereas both animals expend the same

amount of energy for covering the ground (90 kcal) and the same 41 kcal for basal energy over the hour. Similarly, an excitable dog such as a Terrier that stands up all day and is in constant motion around a house at low speed will require more energy relative to its weight than a Greyhound that lies down most of the day and runs around rapidly for 30 seconds in the yard two or three times daily.

In addition to the energy required for standing and horizontal motion, additional energy is needed to support the change in kinetic energy associated with acceleration. Thus, a Greyhound requires three times as much energy for acceleration during the first few seconds of a race than it does while maintaining its pace during the rest of the race, i.e., approximately 3 kcal/kg BW for each horizontal kilometer as it accelerates up to almost 70 km/h, but only 1 kcal/kg BW for each kilometer traveled while it continues to run at more than 40 km/h. This latter value is the same amount of energy required by dogs of similar BW that run more slowly (NRC 2006).

Dogs in jumping trials probably require the same amount of energy for acceleration as Greyhounds during the few seconds before takeoff but this need for increased energy is very brief. Agility dogs will require extra energy for acceleration several times during a trial, but on each occasion the increased energy will be required only briefly and the size of the increase is likely to be more modest because agility dogs do not accelerate to such high speeds as Greyhounds. Thus, dogs undertaking short-distance sprint exercise over distances less than 2 km such as Greyhounds, retrieving gun dogs, agility dogs, and jumping dogs require relatively little energy to support activity, whereas dogs undertaking endurance exercise for many hours over long distances such as sled dogs or hunting dogs require much more energy.

Dogs also require additional energy as they gain potential energy running uphill. The energy required by dogs to overcome gravity on a slope of up to 20% has been variously measured to be between 5 and 14 kcal/kg BW for each vertical km in height gained (NRC 2006). Then dogs are able to recoup some of that potential energy as they run downhill again. If muscle were perfectly efficient, then dogs would be able to recoup all the extra energy for climbing when they ran downhill again, but dogs are less than 40% efficient in converting muscle energy so increased energy is needed for running uphill and downhill. Dogs are even less efficient at recouping potential energy when running down a steep slope (20% or more) so the increase in energy requirements for traveling up and down hill is greater when the terrain is steep.

Energy requirements also increase proportionately with the work required when carrying or pulling a load. For a dog carrying a load, energy expenditure increases in proportion to the increase in body mass so that a load that increases body mass by 10% requires a 10% increase in energy expenditure. The energy required for pulling a load has not been measured but is probably three times the work of traction as muscle is 30% efficient in most species (Blaxter 1989).

In addition, energy is required for running over rough terrain, for overcoming wind resistance, and for undertaking other activities such as swimming, jumping, playing, stretching, grooming, eating, and drinking, but the energy requirements for those activities have not been determined. Furthermore, dogs become extremely excited at the prospect of exercise (Greyhound heart rates increase fivefold before a race), which will increase energy utilization. Body temperature also increases during exercise so dogs have to expend energy after a race to lose body heat by panting.

Theoretically, therefore, it should be possibly to estimate the energy required for activity by multiplying the energy required for each activity by the duration of each activity. The duration and intensity of activity is difficult to measure, however. Accelerometers, pedometers, and heart rate monitors might be used to measure activity intensity and duration in dogs or cats, but even should the energetic equivalency of heart rate or accelerometer readings be determined, the individual variation in energy required for those activities is likely to be large. Any energy required for activity must be added to basal energy requirements, which are also extremely variable among individuals. The energy requirements of an individual exercising dog will not be determined by calculation, therefore, in the near future.

For the time being, an estimate of ME requirements and the amount to feed to provide that ME can only be made based on the mean field metabolic rate of free-living dogs undertaking comparable amounts of exercise (Table 4.1; Fig. 4.1). The amount fed must then be adjusted so that a dog maintains a lean BCS. When making this estimate, however, it is important to consider the duration of any activity, the distance traveled, the terrain, and the load that the dog is pulling or carrying and not the speed of travel. It is also important not to rely on classifications such as working dog or pet. Activity varies in all dogs, regardless of background, with the degree of confinement, time of day, ambient temperature, extent of human and canine contact, and among dogs of different sizes, ages, and breeds. Both pet dogs and working dogs tend to be inactive

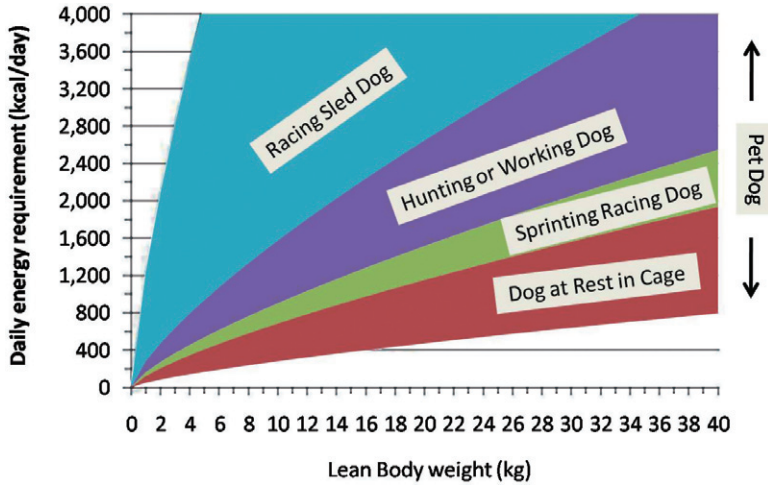

Fig. 4.1. Daily metabolizable energy requirements of dogs undertaking different types of activity. The requirements are represented as ranges for each body weight to reflect the great individual variation shown by dogs of similar weight that undertake similar amounts of activity. The energy requirements of pet dogs encompass a wide range because the duration of pet dog activity varies widely. Dogs that spend most of each day lying down require less energy than dogs that are always active. Sprinting dogs running short distances need less energy than working dogs running longer distances more slowly.

or asleep for more than 60% of each day, and most pet dogs and some working dogs undertake very little additional exercise. Such dogs require little more than basal amounts of energy plus energy for the assimilation of food (approximately 10% increase) for a total of approximately 84 kcal/kg $BW^{0.75}$ daily (NRC 2006). On the other hand, some pet dogs and many working dogs are active for many hours daily, and sled dogs may require up to 15 times that amount of energy daily during a long-distance race. Training does not alter the energy required to maintain any speed so estimates based on the values in Table 4.1 can be used in untrained dogs. Training does increase stamina, however, so untrained dogs are likely to be less active and the intensity of exercise undertaken by an untrained dog will be limited.

TYPES OF EXERCISE AND NUTRIENT REQUIREMENTS

The dietary protein, fat, and carbohydrate requirements of dogs *are* affected by the speed of running *and* the degree of training. Thus, dogs that run very rapidly over a short distance using mostly anaerobic metabolism have different requirements than dogs that run more slowly over long distances using primarily aerobic metabolism. The requirements of untrained pet dogs that only exercise occasionally also differ from those of athletic dogs that undertake intense exercise many times weekly. To understand these differences, it is necessary to understand where an animal obtains energy to support activity.

Initially, energy comes from the high-energy phosphate bond of ATP within muscle buffered by the high-energy phosphate bond of creatine phosphate. The energy from these high-energy phosphate bonds is immediately available, but stores are small, and the energy of ATP has to be constantly replenished either from the anaerobic metabolism of carbohydrate or the aerobic metabolism of carbohydrate and fat. Unfortunately, the rapidity with which energy can be made available from glucose (stored as glycogen) and from fat is inversely proportional to the size of the energy store available (Hultman et al. 1994). Thus, the anaerobic metabolism of glucose can generate energy relatively rapidly but provides only two molecules of ATP from each molecule of glucose and generates lactic acid in the process. Access to oxygen increases the yield of ATP from glucose up to 19 times but provides energy less rapidly, and glycogen can become exhausted at the end of a long run because stores of glycogen are limited. Fat provides an almost inexhaustible source of energy but can deliver energy only at a slow rate, which limits the speed of run that can be sustained. Thus, the duration of the

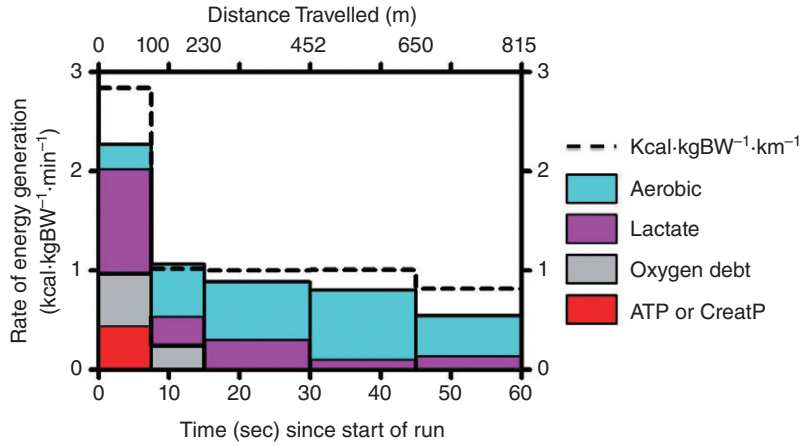

Fig. 4.2. Sources of energy for a Greyhound during sprint exercise. High-energy phosphate bonds in ATP and creatine phosphate (CreatP), alactacid oxygen debt (Oxygen debt), and anaerobic metabolism of glucose to lactate (Lactate) deliver energy rapidly to support the high-energy requirements for acceleration during the first 100 m of a run. Subsequently aerobic metabolism (Aerobic) provides most of the energy for the rest of the race when anaerobic sources of energy have been exhausted. Adapted from Staaden 1984 as described in the National Research Council (2006).

ability to run fast (stamina) is limited by the availability of glycogen. Both people and animals are unable to accelerate at the end of a long-distance race because muscle glycogen is no longer available to support more intense activity.

Dogs differ from human beings in that dogs are adapted for long-distance running using the aerobic metabolism of fat and derive twice as much energy from fat oxidation both at rest and during exercise compared to human beings (McLelland et al. 1994; de Bruijne, Altszuler et al. 1981; de Bruijne and de Koster 1983). Dog muscle does not contain the anaerobic, easily fatigued type IIb fast twitch fibers found in animals such as cats, which are adapted to sprinting. Dog muscle contains only fibers with a high aerobic capacity that are fatigue resistant, i.e., type I slow twitch fibers that rely more on aerobic than anaerobic metabolism and type IIa fast twitch fibers that rely more on anaerobic than aerobic metabolism (Gunn 1978). Dogs store more glycogen and fat in muscle and also can supply more fatty acids to the tissues because albumin binds more free fatty acids in dogs than in less aerobic species (McLelland et al. 1994).

Dogs at rest derive energy almost equally from the oxidation of fat and glucose but when trained dogs start to walk and run, glucose oxidation increases only slightly and most of the increased energy comes from fat oxidation. Then, as the intensity of exercise increases, the supply of oxygen becomes limiting and lactic acid is produced, which increases the concentration of lactic acid and limits utilization of fat. Thus, trained dogs that undertake exercise below the maximum rate of oxygen utilization (VO_2 max), so-called submaximal exercise, rely more on the oxidation of fat, whereas dogs undertaking exercise above their VO_2 max, so-called supramaximal exercise, rely to a greater extent on the anaerobic and aerobic metabolism of glucose.

Racing Greyhounds undertake supramaximal exercise (see Fig. 4.2). They develop a marked lactic acidosis (24–34 mmol/L) after running for less than a kilometer at speeds of over 40 km/h for less than a minute (NRC 2006). Almost all other exercising dogs perform submaximal exercise because very few dogs can be persuaded to perform supramaximal exercise when running on a flat surface (Seeherman et al. 1981). Lactic acid production does increase slightly in dogs running submaximally, but lactic acid utilization also increases so that concentrations in the blood at the end of a run remain unchanged (approximately 1 mmol/L) or increase only slightly (approximately 3 mmol/L). This modest change in lactic acid concentrations after exercise has been demonstrated in dogs running on a treadmill, undertaking a sled dog race, or an agility trial or retrieving (Seeherman et al. 1981; Matwichuk et al. 1999; Rovira et al. 2007; Young, Mosher et al. 1959; Hinchliff et al. 1993). Rather than becoming

acidotic, dogs undertaking submaximal exercise tend to become alkalotic because they have to pant to maintain body temperature.

Protein and amino acid synthesis and catabolism increase in exercising dogs to support the anatomic changes associated with training and also to support gluconeogenesis in dogs undertaking long-distance submaximal exercise. Dogs initially use glycogen as a source of glucose during submaximal exercise but increase gluconeogenesis from protein after about 30 min (Wasserman et al. 1992). Dogs running for more than 30 min, therefore, require much more protein in their diet than dogs such as Greyhounds, which run for much shorter periods of time (Reynolds et al. 1999; Hill et al. 2001).

Terms such as "sprint," "marathon," "short-distance," and "long-distance" are not helpful in this context because such terms mean very different distances and speeds for Greyhounds or sled dogs. Greyhounds never race for more than a kilometer and indulge in supramaximal exercise in both "sprint" and "marathon" races, whereas sled dogs race over many kilometers and indulge in submaximal exercise in both "sprint" and "long-distance" races. When deciding how to feed an athletic dog, therefore, it is more important to consider whether it is undertaking anaerobic supramaximal exercise or aerobic submaximal exercise. As a general rule, most dogs should be considered to perform submaximal exercise. Only racing sight hounds or dogs running on a steep slope or pulling heavy loads are likely to approach or exceed their VO_2 max.

THE IMPORTANCE OF TRAINING

Most nutritional studies of exercising dogs have used dogs that have undergone some form of training for the exercise that they are required to perform. In contrast, most pet dogs are not trained and often only undertake intense exercise intermittently at the weekend. It is better, however, to exercise dogs more frequently than to change their diet. Training does not affect energy requirements but has marked effects on stamina (Musch 1985). Training increases heart size so that heart rate is decreased during exercise while blood flow to the tissues is increased. Untrained dogs have a 30% lower VO_2 max and produce more lactic acid, which limits the use of fat as an energy source and increases the rate of decline in blood glucose during exercise (Paul and Holmes 1975). Thus, the improvement in stamina associated with feeding more fat to trained dogs may not occur in untrained dogs. Training also increases olfactory acuity and reduces free radical formation and may reduce the risk of injury (NRC 2006).

NUTRITIONAL RECOMMENDATIONS FOR DOGS UNDERTAKING DIFFERENT TYPES OF EXERCISE

The minimum requirement of a nutrient has been defined by the National Research Council as "the minimal concentration or amount of a bioavailable nutrient that will support a defined physiological state" (NRC 2006). To determine the minimum requirement, performance, health, or some other suitable measure of well-being must be measured as the amount of a nutrient is gradually increased in the diet. Unfortunately, no minimum requirements have been established for exercising dogs because the effect of gradually increasing nutrient density on performance or health has not been assessed for any nutrient in active dogs. Most studies have only compared two concentrations of nutrient or else the differences between nutrient concentrations have been too large to accurately establish a minimum requirement. Thus, any recommendation for an exercising dog (Table 4.2) only represents an adequate intake, which has been defined by the National Research Council as the lowest concentration or amount of a nutrient that published studies report has sustained trained dogs

Table 4.2. Adequate Intakes[1] for Dogs That Undertake Long-Distance Aerobic Exercise and Short-Distance Primarily Anaerobic Exercise.

Nutrient	Long Distance Aerobic	Short Distance Mostly anaerobic
Protein	90 g/1,000 kcal (40% AF[2])	60 g/1,000 kcal (27% AF)
Fat	59 g/1,000 kcal (27%AF)	36 g/1,000 kcal (16%AF)
Carbohydrate	0	105 g/1,000 kcal (47%AF)
Water[3]	2.4 L/1,000 kcal	2.4 L/1,000 kcal
Sodium	1 g/1,000 kcal	1 g/1,000 kcal
Potassium	1 g/1,000 kcal	1 g/1,000 kcal
Calcium	3 g/1,000 kcal	3 g/1,000 kcal
Phosphorus	3 g/1,000 kcal	3 g/1,000 kcal

[1]Diets containing these adequate intakes or more have been reported to sustain trained dogs repetitively undertaking the type of exercise described, but lower amounts may also sustain satisfactory performance.

[2]% AF: the equivalent adequate intake as % as fed is shown in parentheses assuming the diet is dry high fat diet containing 4.5 kcal/g as fed.

[3]Average requirements are 1.2 L/1,000 kcal, but some dogs consume twice that amount.

(usually sled dogs or Greyhounds) that undertake regular exercise. It is quite possible, however, that lower concentrations than those listed could support exercising dogs, especially if the type of exercise is less intense than that performed by sled dogs and Greyhounds. Furthermore, nutrient intake will increase as food intake increases to support increased energy needs. Requirements for some nutrients may not increase in parallel with energy requirements as exercise increases, so it is possible that lower concentrations of a nutrient than those recommended for the maintenance of dogs that undertake more modest amounts of exercise may maintain a more active dog that consumes increased amounts of food to supply its increased energy needs. Conversely, sedentary dogs may need to consume more nutrient-dense foods than are required for maintenance of modestly active dogs.

There are no studies of the nutrient requirements of untrained dogs that exercise so a recommendation cannot be made for untrained dogs that are active. Nevertheless, most pet dogs are untrained and only exercise infrequently at the weekend. Their stamina will be low, so pet dogs are unlikely to undertake much more activity than laboratory dogs. As most nutrient requirements for dogs have been determined based on studies using untrained laboratory dogs that are only moderately active, nutrient requirements established for adult and growing dogs should provide adequate nutrition for most untrained pet dogs. Owners of dogs that perform more exercise than a laboratory dog in a kennel with a run should train their dogs by gradually increasing the frequency and intensity of exercise. Training is likely to improve performance and health more than any change in diet. Then, once a dog is trained, recommendations made in this chapter will become relevant.

Long-Distance Submaximal Aerobic Exercise

Dogs running long distances have more stamina when adapted to very-high-fat diets because they use muscle glycogen more slowly when fed a higher-fat diet (Reynolds et al. 1995). This contrasts with human long-distance athletes, whose stamina increases when human athletes consume a high-carbohydrate diet. Dogs undertaking long-distance exercise also develop a "sports anemia" and suffer more injuries unless fed a high-protein diet containing an adequate balance of amino acids (Reynolds et al. 1999). The source of this protein must be very digestible to limit the amount of undigested protein entering the large intestine. Excess protein or fermentable carbohydrate entering the large intestine will be fermented to short-chain fatty acids and can cause an osmotic diarrhea (Taylor et al. 1958; Orr 1966).

Guaranteed Analysis		
Crude Protein	26.0%	minimum
Crude Fat	18.0%	minimum
Crude Fiber	3.0%	maximum
Moisture	10.0%	maximum
Ash	5.5%	maximum

Fig. 4.3. Typical guaranteed analysis on label of a higher-protein, higher-fat commercial dry dog food suitable for feeding an active pet dog. Note that this food does not contain enough protein and fat for a working or hunting dog running long-distances daily over many hours. Such dogs should be fed a high-protein, high-fat canned diet. Compare the guarantees on different canned diets to find a canned diet that contains the most fat and protein. Do not compare the guarantee on canned and dry diets. Dry diet guarantees are higher than canned diet guarantees because dry diets contain less water, but they also contain less protein and fat when the difference in water content is taken into account.

Dogs running long distances do not require digestible carbohydrate provided there is enough dietary protein to support gluconeogenesis. It is unclear, however, whether there is a need for indigestible carbohydrate. Short-chain fatty acids produced by anaerobic fermentation support colonic mucosal health, but it has not been established whether soluble fiber is needed in the diet in addition to undigested protein and undigested starch as a substrate for that fermentation. Large amounts of fiber are not desirable, however, because increased fiber increases the weight of the colon and water loss in the feces.

For most active dogs, therefore, that undertake moderate amounts of activity, a high–fat, high-protein dry commercial diet should provide sufficient protein and fat (see Fig. 4.3). Dog owners should select a dry diet with the highest guarantee on the label for both protein and fat. As the frequency and duration of exercise increase, however, dry diets may not provide enough protein and fat so a high-protein, high-fat canned diet should be added to provide the extra energy the dog will need as well as the extra protein.

Short-Distance Supramaximal Anaerobic Exercise

Dogs undertaking sprint exercise such as Greyhounds do not require as much protein or fat. Performance has decreased when dietary protein has increased in substitution for dietary carbohydrate (Hill et al. 2001). The duration of exercise is short, glycogen stores are unlikely to be

depleted, and protein is not needed to support gluconeogenesis. Both lower and very high amounts of dietary fat have been associated with reduced performance, also, but the ideal amount of fat and carbohydrate to include in the diet has not been established (NRC 2006). Currently, a diet is recommended that contains only moderate amounts of protein (60–70 g protein/1,000 kcal ME) and fat (36–50 g fat/1,000 kcal ME) but the amount of fat may need to be adjusted for optimum performance. Both canned and dry diets are available, which meet this specification.

Fluid and Electrolyte Requirements, Hydration, and "Sports Drinks"

Dogs require unlimited and frequent supplies of water before, during, and after exercise, but do not require extra sodium or other electrolytes or vitamins. Dogs do not sweat. Sports drinks designed for humans that contain sodium and electrolytes are not recommended for dogs that exercise and can reduce performance (Young, Schafer et al. 1960). Some glucose may be added to the water after exercise to replenish glycogen stores, but the exact amount to add is uncertain. There is also no evidence that other, so-called ergogenic nutrients, have any benefit.

Adequate hydration is essential for optimum athletic dog performance. Body temperature increases during exercise and limits activity in dogs (Kozlowski et al. 1985). Very high body temperatures can result in tissue damage, especially damage to the intestine and kidneys, that can be life threatening, and should be avoided at all costs. Keeping dogs cool by using cold packs and exercising dogs in cold ambient temperatures allows dogs to exercise for longer periods of time (Kozlowski et al. 1985; Kruk et al. 1985). Dehydration increases the rate of increase of body temperature during exercise and reduces the duration and intensity of exercise of which dogs are capable (NRC 2006). Maintaining hydration improves stamina, therefore, and reduces the risk of life-threatening hyperthermia.

Water loss by evaporation for cooling increases during exercise with increased ambient temperature. Urine production also increases as food intake increases to support the energy needs of exercise in proportion to the amount of salt and urea (from protein) that must be excreted. Average water requirements increase from 0.5 mL/kcal at cold ambient temperatures to 0.6–1.2 mL/kcal at room temperature (depending on the amount of sodium and protein in the diet) and 1.8 mL/kcal in obese dogs (NRC 2006). Dogs should be offered twice these mean amounts, however, because individual dogs may require double the average amount.

Dogs become dehydrated intermittently over time because water is lost continuously in urine and by evaporation, but dogs drink water only intermittently. Sedentary dogs do not usually anticipate the need to drink and only drink after losing about 0.5% of BW, but dogs will maintain their hydration during exercise by drinking regularly if given the opportunity (O'Connor 1975). Thus, water should be made available to dogs before exercise, at intervals during, and shortly after exercise.

Because dogs lose water but little sodium during exercise, their blood becomes hyperosmolar. Drinking water without any solute corrects this hyperosmolality immediately, whereas drinking water containing salt or glucose will not correct the hyperosmolality, and dogs will continue to wish to drink more (Ramsay and Thrasher 1991). It is best, therefore, to correct dehydration during exercise with water containing no solute and to provide glucose containing water after exercise to facilitate replenishment of glycogen stores.

Commercial sports drinks sold for human athletes should not be offered to exercising dogs. Dogs do not sweat except on their footpads. The increase in salt loss when dogs pant and drool during exercise is small so there is little increase in a dog's requirement for salt during exercise. Any salt consumed in drinking water will have to be excreted in the urine, which will increase the rate of water loss and may exacerbate dehydration. The adequate intake for both sodium and potassium recommended by the National Research Council for exercising dogs is 1 g/1,000 kcal. Most commercial diets will provide sufficient sodium and potassium without the need for supplementation.

Antioxidants

Oxidation occurs as a normal process within mitochondria as energy is made available during exercise. More oxidation occurs as the amount of energy required increases, but regular exercise also increases the antioxidant defense mechanisms within the body. Antioxidant nutrients, such as vitamin E, are an essential component of the diet of exercising dogs, therefore, to minimize oxidation during exercise. Requirements for antioxidant vitamins also increase with the amount of fat and with the amount of polyunsaturated fat in all diets, especially if the food is to be stored for any length of time. It remains to be determined, however, whether dogs that exercise require any more antioxidant nutrients than sedentary dogs. Antioxidant requirements for dogs that exercise regularly may even be less than for sedentary dogs that only exercise intermittently at the weekend, and it is better to exercise

dogs more regularly than to recommend any increase in antioxidant vitamins in the diet.

Vitamins, Trace Minerals, and Other Essential Nutrients

Requirements for some B vitamins, such as thiamin, are likely to increase and decrease in proportion to energy requirements, whereas requirements for vitamin B6 (pyridoxine) tend to vary with protein intake. Most commercial diets contain an excess of B vitamins to compensate for losses during processing, however. Furthermore, intake of these vitamins will increase and decrease proportionally as food intake varies with energy requirements. It is unlikely, therefore, that B vitamins will be deficient in most commercial diets, and supplementation with these vitamins above that already present in the diet is almost certainly unnecessary.

It is also almost certainly true that the requirements for calcium, phosphorus, and other minerals do not increase directly in proportion to energy requirements, so the amount of minerals in the diet of sedentary dogs should be adequate for exercising dogs. Thus, on the contrary, there is a potential for excess intake of calcium and trace minerals by dogs that take in large amounts of food because of their very high energy requirements. The amount of trace minerals in the diet of dogs undertaking large amounts of exercise should be kept close to the minimum requirement and should probably not be increased as the amount of fat is increased in the diet.

Other Nutritional Supplements

There is currently no experimental evidence that so-called ergogenic nutrients improve the performance of exercising dogs. Adding creatine to the diet of dogs has not been shown to increase the amount of creatine in muscle or performance. Dimethylglycine and diisopropylammonium dichloroacetic acid reduced the race time of Greyhounds (Gannon and Kendall 1982), but this beneficial effect was probably due to dichloroacetic acid, which reduces lactic acidosis. Addition of dichloroacetic acid to the diet is not recommended, however, because dichloroacetic acid is toxic to dogs in small doses (Cicmanec et al. 1991). Glucosamine and other nutrients designed to moderate the effects of osteoarthritis may be of benefit in exercising dogs with this condition, but there is currently no evidence that such nutrients prevent osteoarthritis.

Time of Feeding

Food deprivation does not compromise the performance of dogs undertaking endurance exercise (Young 1959). Glucose given before or during exercise minimizes the decline in blood glucose concentrations during exercise and minimizes the increase in body temperature during exercise, whereas glucose given after exercise promotes the repletion of muscle glycogen. The amount of glucose that should be administered is uncertain, however, because the amounts of glucose given to dogs have varied widely from 1.5 mg to 1.5 g/kg BW (Reynolds et al. 1997; Wakshlag et al. 2002). Dogs should not be fed food containing fat immediately before or during intense exercise. Consumption of food directs blood toward the intestine and can compromise performance while exercise compromises intestinal function. Ideally, dogs should be fed shortly *after* intense exercise when the dog's excitement has abated.

SUMMARY

- Regular exercise training more than any change in diet will improve the performance of an exercising dog.
- Active dogs should be fed enough food to maintain a lean body condition.
- Dogs mostly perform aerobic exercise.
- Dogs exercising for more than 30 min require extra protein in their diet.
- Dogs undertaking long-distance exercise require extra fat in their diet.
- Commercial high-fat, high-protein dry dog foods should provide enough fat and protein for most active dogs.
- Working or hunting dogs should have the extra energy they require supplied by commercial high-protein, high-fat canned diets containing little carbohydrate.
- Active dogs should always have free access to water to maximize performance.
- Water given to active dogs may contain some glucose but not other nutrients such as salt.
- Dogs should not be given human sport drinks.
- There is currently no evidence that supplements should be fed to active dogs if they are fed a balanced diet.

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Nutraceuticals and Dietary Supplements

5

David A. Dzanis

INTRODUCTION

It is estimated that from 10% to 33% of the companion animals (dogs, cats, and horses) in the United States receive a daily dietary supplement, with approximately 90% of practicing veterinarians dispensing supplements in their practice (Freeman et al., 2006; Bookout and Khachatoorian, 2007; NRC 2009). This is not necessarily a recent phenomenon, as commercial dietary supplements have long been available for use in animals. Historically, use of supplements was mostly limited to essential dietary nutrients such as vitamins and minerals, generally meant to augment or balance a poor-quality, incomplete, or otherwise inadequate diet. Even with the advent of "complete and balanced" pet foods (circa 1960s), sales of dietary supplements continued, if anything offering the animal owner assurances that nothing of nutritional importance was inadvertently excluded from the diet. However, the past decade has seen a great increase in the numbers and types of dietary supplements for animals, for the most part a reflection of the similar growth in the human dietary supplement market.

Today's animal dietary supplement market is inundated with products of all conceivable types, from vitamins and minerals, to herbs and botanicals, antioxidants, chondroprotective agents, and probiotics. The term "nutraceutical" was coined to describe many of these products. While it has no formal definition, nutraceuticals are typically dietary supplements that are intended for health benefits beyond prevention of essential nutrient deficiencies.

It is inaccurate to say that dietary supplements are "not regulated by the government," as is sometimes reported in the public media. Rather, they are theoretically subject to considerable regulatory scrutiny, but it is the lack of ability to effectively monitor and control what is on the market that leaves the impression of it being "unregulated." In any case, it is a fact that not all animal supplement products on the market are wholly in compliance with applicable law. As a result, many commercial products may contain substances for which safety and utility have not been established, or their labels may bear poorly supported if not totally unsubstantiated claims. Considering the current widespread use of dietary supplements and nutraceuticals for animals, it is prudent for the veterinary practitioner to be familiar with the gaps in regulation of dietary supplements so that he or she may better critically evaluate ingredients and claims prior to dispensing products to clients.

REGULATION OF DIETARY SUPPLEMENTS

Definitions, Abbreviations and Acronyms

AAFCO: Association of American Feed Control Officials. A nongovernmental organization (but whose members must be state, federal, or foreign government employees) that establishes model animal feed laws, regulations, and ingredient definitions, which then may be adopted by individual state agencies charged with regulation of animal feed.

Animal Dietary Supplement: As defined by the National Research Council (NRC), a substance for oral consumption by horses, dogs, or cats, whether in/on feed or offered separately, intended for specific benefit to the animal by means other than provision of nutrients recognized as essential, or provision of essential nutrients for

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intended effect on the animal beyond normal nutritional needs, but not including legally defined drugs (NRC 2009).

CVM—Center for Veterinary Medicine: Part of the Food and Drug Administration (FDA) responsible for interstate regulation of animal foods and drugs.

Dietary supplement: As defined in part by the Dietary Supplement Health and Education Act (DSHEA), a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients [Title 21 United States Code Sec. 321(ff)(1)].

Drug: As defined in part by the Federal Food, Drug, and Cosmetic Act (FFDCA), an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals [Title 21 United States Code Sec. 321(g)(1)].

DSHEA: Dietary Supplement Health and Education Act of 1994.

FDA: United States Food and Drug Administration. It is the federal agency responsible for regulation of foods and drugs in interstate commerce.

FFDCA: Federal Food, Drug, and Cosmetic Act of 1938.

Food: As defined in part by FFDCA, articles used for food or drink for man or other animals [Title 21 United States Code 321(f)].

Food additive: As defined in part by FFDCA, any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food if such substance is not generally recognized as safe (GRAS); except that such term does not include a dietary supplement [Title 21 United States Code Sec. 321(s)].

GRAS: "Generally recognized as safe." As defined in part by FFDCA, a substance generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use [Title 21 United States Code Sec. 321(s)].

NASC: National Animal Supplement Council. A trade organization comprising manufacturers of dietary supplements for companion animals (and associated industries).

NRC: National Research Council. The working arm of the National Academies, a private body that advises the United States federal government on matters related to health and science issues.

Nutraceutical: No official definition. A portmanteau of "nutrition" and "pharmaceutical," generally applied to dietary supplements intended for specified therapeutic effects.

The Dietary Supplement Health and Education Act

The Dietary Supplement Health and Education Act of 1994 (DSHEA, typically pronounced "dee-shay") dramatically changed the regulatory framework upon which dietary supplements may be distributed in the United States. The market for dietary supplements for both human and animal consumption grew tremendously as a result of this legislation. To appreciate the impact of the Act, the applicable law prior to DSHEA must first be understood.

The prevailing law under which both foods and drugs for human and animal use are subject is the Federal Food, Drug, and Cosmetic Act of 1938 (FFDCA). Under the law, the distinction between a "food" and a "drug" largely depends on what claims are associated with the product, i.e., for what purpose the product is intended by the manufacturer or distributor. While the statutory definition of "food" (see definitions, above) is admittedly vague, a precedent-setting court ruling established a "common sense" definition, i.e., as an item consumed "primarily for taste, aroma, or nutritive value" [NutriLab, Inc. v. Schweiker, 713 F.2d 335 (7th Cir. 1983)].

On the other hand, the statutory definition for "drug" includes any article *intended* to treat or prevent disease or to affect the structure or function of the body in a manner distinct from provision of qualities normally ascribed to food, e.g., nutritive value. As a result, any product, even those containing only common food ingredients, can be subject to regulation as a drug under the law if the claims associated with the commercial distribution of the product indicate or imply an intent to offer it as a drug.

For example, a bottle of water, perhaps flavored and/or fortified with some vitamins and minerals, may be assumed to be food. Claims regarding the effect on the structure or function of the body by virtue of the product's recognized nutritive value, such as "water helps maintain a healthy body" or "with calcium and vitamin D for strong bones," would not deviate from that assumption. However, if the bottle's label bore claims such as "for treatment of diar-

rhea" or "cures osteoporosis," those may be construed as intent to offer the product for therapeutic reasons, i.e., as a drug.

The regulatory category into which a substance is placed affects its requirements for legal distribution. A drug is held to a higher standard and with only a few exceptions must be proven by the manufacturer to be safe and effective for its intended use prior to marketing. This is typically accomplished through submission of data to FDA for its review and approval. The approval processes can be arduous, time-consuming, and costly. Drugs on the market that do not undergo pre-market clearance would be considered "adulterated" drugs, and as such are subject to enforcement action by FDA. Such actions could include seizure and destruction of the product in question, an injunction against the company, or in the most egregious cases, criminal charges against the owners or officers of the company.

On the other hand, foods do not require pre-market clearance from FDA. However, this presumes that the food soley comprises ingredients that are "generally recognized as safe" (GRAS) substances or approved food additives. A list of GRAS substances appear in FDA regulations, but that category may also include many ingredients that have, through common usage, established a long history of safe use in food, even though not expressly codified as such [Title 21 Code of Federal Regulations Sec. 582.1]. GRAS substances are only GRAS for their intended uses. For example, a GRAS anticaking agent is not GRAS for intended use as a mycotoxin binder (Benz 2000).

Food additives are substances that are not GRAS and must undergo an approval process to demonstrate safety and utility prior to marketing. There are occasional exceptions to the rule. For animal feed ingredients, these exceptions include those that undergo the rigorous, albeit officially informal, process wherein an Association of American Feed Control Officials (AAFCO) feed ingredient definition is established [the Center for Veterinary Medicine (CVM) reviews data for new AAFCO ingredients similar to the way it reviews food additive petitions, so that while not officially "approved," these ingredients are allowed on the market under enforcement discretion policies]. Foods containing unapproved food additives (i.e., not GRAS, approved food additives, or AAFCO-defined ingredients) would be considered "adulterated" foods and subject to enforcement actions similar to that for adulterated drugs.

Prior to DSHEA, supplements consisting of recognized essential nutrients such as vitamins and minerals generally fell into the "food" category. However, any inclusion of a substance that was not GRAS or an approved food additive, such as many herbs and botanicals, antioxidants, glucosamine and chondroitin sulfate, or similar substances, could easily cause the product to be an adulterated food. Also, any claims relating to treatment or prevention of disease or effect on the structure or function of the body outside of classical nutritional precepts would most likely subject the product to possible enforcement action as an adulterated drug.

DSHEA changed the regulation of dietary supplements in several ways. For one, it amended FFDCA so that a substance in a product that met the statutory definition of "dietary supplement" (see Definitions, above) was *not* a food additive, hence not subject to pre-market clearance requirements. The Act included a grandfather clause, so that any substance in or marketed as a dietary supplement prior to passage of DSHEA (in compliance with FFDCA or not) was included in this definition. There are provisions in the law that give FDA power to remove unsafe dietary supplements. However, the Act effectively shifted the burden from a manufacturer having to prove a substance was safe prior to use to FDA having to prove a substance was unsafe before enforcement action could be taken. As a result, many substances that had no historical use as food or legitimate nutritional purpose could now be included in products deemed to be dietary supplements without regulatory recourse.

DSHEA also shifted the paradigm for what constituted a drug claim. Claims to treat or prevent a disease still are not allowed under DSHEA. However, DSHEA does provide for "support" claims, or claims to affect the structure or function of the body beyond its food qualities, i.e., not necessarily limited to those pertaining to normal nutrition. For example, a claim for the herb saw palmetto in a dietary supplement to "help maintain prostate health" may be allowed, despite the fact that its purported effect on prostate health is not related to the provision of a vitamin, mineral, or similarly recognized essential nutrient. One condition of making such a support claim is the inclusion of the disclaimer: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose treat, cure or prevent any disease." There are other labeling requirements stipulated, such as identification as a "dietary supplement" and the presence of a "Supplement Facts" box (in lieu of a "Nutrition Facts" box as required on other human food product labels).

Although a dietary supplement is still "food" under FFDCA, DSHEA defines a distinct subcategory of food with unique regulatory privileges not afforded other foods, and dietary supplements in pill, powder, or liquid form

may contain ingredients or make claims not granted to foods in "conventional" form. For example, the herb echinacea may be marketed in pill form as a dietary supplement, notwithstanding the fact that the herb is neither GRAS nor an approved food additive. Further, its labeling may bear claims such as to "help maintain a healthy immune system," purported by advocates (but not claimed on the label) to reduce the incidence or severity of colds. However, DSHEA would not apply to use of the same herb in a chicken soup product. No claims regarding functionality of echinacea in chicken soup would be tolerated. However, even without claims, echinacea would be an unapproved food additive, and the chicken soup product an adulterated food.

Animal Products and DSHEA

In 1996, CVM published a notice in the Federal Register opining that DSHEA did not apply to products intended for animals (FDA 1996). The reasons for this opinion included the fact that DSHEA and its supporting documentation hint only at use of products "in man," or for "improving health status of United States citizens," with no indication for use of supplements in animals. Therefore, CVM concluded that it was neither contemplated by nor the intention of Congress for DSHEA to apply to products intended for animals other than humans.

CVM further concluded that Congress' exclusion of application of DSHEA to animal products is prudent. One of the driving presumptions leading to the passage of DSHEA was that there was a long history of use of herbs and similar substances for their health benefits wherein reasonably safe levels of intake in humans could be established. However, there is a paucity of data, historical or otherwise, relative to the effective and safe use of dietary supplements for animals compared to that for people. Also, while the approval process in place for animal drugs and food additives includes review of data to show the absence of unsafe residues in meat, milk, or eggs of animals consuming the substance, applicability of DSHEA would circumvent that safety requirement. Finally, since CVM considers "production" claims (i.e., claims to affect performance, such as weight gain, feed efficiency, or milk yield) to be drug claims requiring pre-market clearance, DSHEA would also unfairly allow manufacturers of dietary supplements for animals to elude that requirement.

Without DSHEA applying to animal products, the existing provisions in FFDCA apply. Therefore, unless a supplement is considered a drug, there is no regulatory distinction between dietary supplements for animals and any other animal feed—all are simply "food." As such, dietary supplements for animals may not contain unapproved food additives, nor may their manufacturers make claims relative to effects on the structure or function of the body unless they pertain to accepted nutritional principles. Further, animal supplements cannot be labeled under the provisions of DSHEA (e.g., no "not evaluated by FDA" disclaimer, no "Supplement Facts" box). In fact, CVM objects to the use of the term "dietary supplement" as it pertains to animal products, as it may falsely imply applicability of DSHEA.

That said, the market is replete with products that appear to violate FFDCA. This is true despite the fact that animal feed products, including dietary supplements, are subject to oversight at both the federal and state levels. As animal feed, there are no registration or pre-market clearance requirements by CVM for animal supplements. Rather, it is the burden of the manufacturer to ensure that the product and labeling is compliant with applicable federal law. However, unless the violative product is brought to the attention of CVM via queries from state feed control officials, the manufacturer's competitors, or members of the public, it may be in interstate distribution for a long time before CVM discovers it and can initiate corrective action.

Animal feeds are also regulated at the state level, generally by the state's department of agriculture or chemist's office. The majority of these states have adopted versions of the Model Bill and Regulations as published by AAFCO. These models represent a consensus among government officials of what constitutes fair and reasonable oversight of animal feed products, but neither AAFCO nor its model rules have any enforcement authority in and of themselves. While every state has and will continue to have different laws and will regulate animal feeds according to its particular statutes, the AAFCO models represent an attempt to establish equivalent rules and uniform enforcement among the individual states. A common misconception is that AAFCO is a trade organization and simply caters to the needs and desires of the animal feed industry. The truth is that while the organization is a private body, its voting members comprise only state, federal, and foreign government employees.

For states that follow the AAFCO models, animal feed products, including animal supplements, must be registered with the state prior to distribution in that state. This typically applies not only to products at retail outlets, but to products shipped into the state via catalog or website

sales as well. Alternatively in some states, companies must be licensed in the state before any products may be distributed, and occasionally both product registration and company licensure is required. In any case, submission of labels for review by the state is the norm. States that find noncompliant products or labeling may deny registration and/or licensure, or demand changes to the product or labeling as a condition of approval for distribution in the state. Often, a state may refer matters regarding unapproved food additives or questionable claims to CVM for resolution.

The rigor of the review can be quite variable. Despite similar laws, products that are found to be noncompliant in one state may be acceptable to another. Much of this depends on the individual state's available enforcement resources and regulatory priorities. Also, notwithstanding equivalent regulations, the interpretation of those regulations may differ between states.

In play at many times, especially in the case of animal supplements, is the concept of "enforcement discretion." This is when a recognized violation is overlooked under certain conditions, either because it is of relative low priority or to provide for uniform enforcement. The best example is the inclusion of glucosamine and chondroitin sulfate in pet food and supplement products. Technically, both substances are unapproved food additives, and their inclusion in a product formulation, even without claims, renders the food "adulterated." In fact, FDA denied a proposal to allow an AAFCO feed ingredient definition for glucosamine after review of submitted data (Bookout and Khachatoorian 2007). Most states, though, permit the inclusion of these substances in companion animal products, in supplement or conventional food form, provided minimum amounts are declared in the guaranteed analysis, and, for dog and cat foods and supplements, are accompanied by the disclaimer "not recognized as an essential nutrient by the AAFCO Dog (or Cat) Food Nutrient Profiles." While overt drug claims are generally prohibited, vague references to functionality, e.g., "to help maintain hip and joint health" are usually tolerated. The Office of the Texas State Chemist has the most rigorous provisions, and, in addition to the stipulations above, requires products to be indicated for adult maintenance of dogs only (i.e., not for puppies or cats), and to be formulated to deliver no more than 15 and 12 mg/kg of body weight per day of glucosamine hydrochloride and chondroitin sulfate, respectively, when fed as directed (http://otscweb.tamu.edu/Laws/PDF/Feed/FdInd-3-17.pdf).

For products in nationwide distribution, denial of registration by one or several states may have a dramatic impact on the manufacturer's ability to distribute product effectively and efficiently. To avoid the need to print separate labels and keep the appropriate labels in the appropriate states, a unique interpretation by one state may require changes affecting all states. Further, changes to address the demands of one state occasionally may cause the product to be noncompliant in another. Therefore, even companies acting in good faith are frequently in a constant struggle with one state feed control official or another and may have difficulties in achieving labeling that is universally accepted.

Some companies may inadvertently avoid, or choose to avoid, this dilemma by simply failing to license themselves and/or register products in a state or states. This may be particularly true for products that are not sold in a physical location in the state, but offered only through catalog or online sales. For some animal supplement companies, this may be due to ignorance of the state's requirements, for others, an intentional means to elude discovery by the state feed control officials of unapproved food additives or the presence of drug claims on the labeling. In either case, a product or company that is not registered or licensed may go undiscovered by regulators and could continue to be distributed unfettered for years.

Many states feed control official offices do conduct random inspections of feed stores, pet stores, grooming shops, veterinary offices, and other retail outlets of animal feed products. Samples may be collected for label review and/or analysis. If the product is unregistered but otherwise found to be compliant with state regulations, remedy may be as simple as requesting the manufacturer to register or license as required. Depending on the extent of any violation found, however, a product may be subject to a "withdrawal from distribution" (also called a "stop sale") order. In some cases, product may be allowed to be retrieved by the manufacturer, but in others, the inventory is seized and ultimately destroyed. However, whether this ever happens depends on circumstance, i.e., the state inspector randomly visits a site and by chance collects a sample. Depending on the size of the inspection program, some retail sites may be visited infrequently, if ever.

Another potential strategy of some animal supplement manufacturers to escape the oversight of state feed control officials is to label the product similarly to an animal drug, not as an animal feed. While CVM does retain jurisdiction for products in interstate commerce whether they are foods or drugs, many states relinquish authority in the case of drugs. Some states do have "animal remedy" laws, but depending on the

organizational structure of the state government, it may or may not be the same people, office, or even department enforcing those laws as those enforcing the animal feed laws.

One trade association, the National Animal Supplement Council (NASC), recommends this "drug-like" type of labeling for its members whose products do not meet FFDCA as a food. (Bookout and Khachatoorian 2007; Dzanis 2009). Its intent is not to subject its members' products to the normal FDA approval process via submission of a New Animal Drug Application, though. Rather, NASC has coined a new term that is not in the regulatory lexicon ("dosage form animal health product") to apply to dietary supplements for animals not in the human food chain. The ultimate intent is for these products to be afforded status as "unapproved drugs of low regulatory priority" by CVM.

For practical reasons, not all drugs allowed on the market by CVM are formally approved via the New Animal Drug Application route. In some cases, CVM may exercise enforcement discretion for products where there are reasonable assurances of safety and efficacy outside of a formal application submission. As a result, some drugs, such as topical agents, animal equivalents to over-the-counter human drugs, and petrolatum-containing cat hairball remedies may be tolerated without approval, contingent with certain provisions. For one, the labeling must conform to CVM policies, including appropriate directions for use and warning statements, and removal of claims regarding function as a "food" or "supplement" or to provide nutrition. The company must register as a drug manufacturer with FDA, and "drug list" its products. Also, the company must follow good manufacturing practices (GMPs) in the manufacture of its products.

Products labeled akin to "drugs" may enjoy privileges not granted dietary supplements labeled as "foods." For one, they may contain ingredients that are not GRAS, approved food additives, or AAFCO-defined. Second, they may bear drug claims, although the extent of such claims would still be subject to CVM's acceptance. On the negative side, since the products are not formally approved drugs, CVM reserves the right to rescind its discretionary policy and take action against the product as an adulterated drug at any time.

NASC has implemented programs to require certain manufacturing and labeling practices of its members, all of which are subject to audit by NASC (Bookout and Khachatoorian 2007; Dzanis 2009). These include mandatory drug listing with FDA and requirements to follow GMP provisions similar to those established for human dietary supplements in FDA regulations. The organization has also instituted an adverse event reporting system for its members, the results of which are made available by NASC to CVM and state feed control officials.

At this time, CVM appears receptive to the idea of marketing animal dietary supplements as drugs. Several compliance policy guides that may serve to address this issue are reportedly under development, one specifically related to glucosamine/chondroitin-containing products and a second related to the marketing of dog and cat products bearing drug claims. Although there has been speculation regarding the content of these documents, to date, CVM has not made the details publicly available.

A potential concern by segments of the pet food industry is that this policy may create an unfair distinction between animal dietary supplements and animal feeds containing the same ingredient. For example, a dietary supplement containing glucosamine may easily be labeled as a drug, whereas by its very nature a complete and balanced pet food label cannot be devoid of "food" claims. It is unclear, then, whether there would still be enforcement discretion for use of glucosamine in pet foods at all once this policy was implemented.

CVM has also recently commissioned a report by NRC to help CVM in its evaluation of the safety of animal dietary supplement ingredients (NRC 2009). CVM recognizes that in the case of many dietary supplements, available safety data are insufficient for some ingredients to be approved through formal means (e.g., New Animal Drug Application, Food Additive Petition). To help address this concern, NRC convened a panel of experts in animal nutrition, pharmacology, and toxicology to deliberate on the issues similarly to an earlier study on the safety of human dietary supplements (Institute of Medicine and National Research Council 2005).

The NRC report provides a working definition for "animal dietary supplement" that is distinctly different from the definition for "(human) dietary supplement" as provided for in DSHEA (see Definitions, above). The DSHEA definition only applies to items offered in "supplement" (i.e., dosage form) versus "conventional food" form, and applies to essential nutrients as well as nonessential substances. However, for the purposes of the report, it was crucial in the NRC definition to include substances regardless of feeding method (either incorporated into the diet or fed separately), and to purposefully exclude recognized dietary essential nutrients for which the existing regulatory oversight is generally sufficient to ensure safety.

The NRC report discusses the current regulation of animal dietary supplements and how it compares to the

regulation of human supplements under DSHEA. Also discussed are the methods available to assess animal dietary supplement safety, the factors affecting their safe use, and the categories of scientific evidence as they relate to assessing the strength of available data. As examples, the safety of several substances (lutein, evening primrose oil, and garlic) is assessed in detail. The report concludes with recommendations to allow CVM (and possibly other parties, including veterinarians) to better assess the safety of ingredients with less than complete information. In that way, CVM can allocate enforcement resources to focus on dietary supplements (whether labeled as food or drug) that represent more serious safety concerns.

USE OF SUPPLEMENTS IN PRACTICE

As with all elements of practice, veterinarians may be legally or ethically liable for adverse events that may stem from using, dispensing, or recommending dietary supplements for their patients. Unlike FDA-approved drugs or food products that meet FFDCA requirements, the use of supplement products that have not or most likely would not pass regulatory muster carries a potentially greater risk for the veterinarian. Provisions in the law that grant the veterinarian authority to employ "extra-label" use of human or animal drugs only applies to approved drugs (http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm100268.htm).

Further, depending on the exact wording of the state's veterinary practice act under which the veterinarian practices, use of dietary supplements may or may not be considered a component of recognized veterinary practice (Scoggins 1998). This may have an impact on the malpractice insurance carrier's determination as to whether a claim against the veterinarian is covered by the policy.

In light of these considerations, it behooves the veterinarian to critically evaluate the rationale for using a dietary supplement, the data supporting this use, and its source. Also, as experience is gained with the use of a particular supplement in practice, timely reassessment of its use is prudent.

Guidelines for Evaluation

Assessment of Need

The veterinarian should establish a sound rationale for use of a dietary supplement before it is administered to the patient. Does the animal have a disease or condition for which a dietary supplement is purported to help? On what basis, and from what source, is this effect claimed? Recommendations or opinions from qualified experts, such as diplomates of a veterinary specialty organization recognized by the American Veterinary Medical Association, and published papers in peer-reviewed journals may be more reliable than those from self-proclaimed authorities on the Internet or elsewhere. Potential conflicts of interest, such as the proponent's financial connection to the company that markets the product, should be considered. In any case, the reasons for using a dietary supplement should be scientifically sound and based on accepted medical principles.

An accurate diagnosis should be vital to this assessment. Diagnostic principles underlying therapeutic use of some supplements, such as herbs, may diverge from conventional veterinary practice (Ramey 2007). A vague indication for use of a supplement, such as "to detoxify the liver," may or may not be appropriate for all cases of hepatic disease, and in fact may be contraindicated for some animals. An understanding of the supplement's mode of action as it pertains to the individual animal's disease process is needed.

Even given a specific, albeit less than definitive diagnosis, the supplement may or may not be indicated. For example, while a functional taurine deficiency may be a cause of dilated cardiomyopathy in dogs of certain breeds or under certain dietary conditions, there are other causes of dilated cardiomyopathy in dogs for which supplemental taurine would have no effect. Ideally, determination of plasma and whole blood taurine concentrations is indicated before supplementation. On the other hand, taurine is considered safe and relatively inexpensive (Sanderson 2006). Thus, if used in conjunction and not in lieu of other appropriate treatment, the effect of taurine supplementation may be diagnostic if not of direct benefit.

Assessment of Evidence

The decision by the veterinarian to use a supplement to address a particular disease or condition should demand ample scientific evidence to show that the supplement is both efficacious and safe for its intended use. Assuming the manufacturer of the dietary supplement has not demonstrated these qualities through submission of a New Animal Drug Application to CVM, the veterinarian must seek other sources of information for these assurances, including the scientific and medical literature.

The supplement manufacturer may cite studies to support use of the product in advertising or on its website. Practitioners should not be shy in asking the manufacturer for access to the studies cited. If a manufacturer is not willing to provide copies of a complete version of the literature cited, it should raise doubts as to the strength of the supporting evidence.

Beyond studies available from the company, independent review of the literature is prudent. Strategies and resources to effectively search online literature databases are described elsewhere (Murphy 2007). Use of Boolean operatives (AND, OR, and NOT) to link key words (e.g., "dogs" AND "taurine") is a common means to limit searches to desired areas of study.

Commonly used resources include PubMed and AGRICOLA, both government-directed sites that offer free access to online searchers. Depending on the source of the material, abstracts, and/or full articles may occasionally be accessed by a link on the search results page. The National Institute of Health Office of Dietary Supplements also provides a free, extensive online database of supplement-related articles. Although the International Bibliographic Information on Dietary Supplements (IBIDS) database was designed as a resource for evaluation of dietary supplements for human consumption, studies on animals as experimental models are often included in searches on particular dietary supplements.

Collection of the pertinent literature is only the first step. Proponents of evidence-based medicine often advocate a ranking system to judge relative values of different types of studies (Holmes 2007). High on the list are systematic reviews and meta-analyses, two methods that analyze a body of studies to reach a scientific consensus. Although they do not provide evidence as strong as the aforementioned, randomized controlled trials and observational studies can also be insightful, as both provide comparisons between groups of subjects to form a conclusion about the effect of a treatment. Multiple or single case reports offer less conclusive evidence of benefit from use of a dietary supplement.

Study in the species of most interest to the practitioner, when available, is generally preferred. While some useful information may be derived from studies conducted in other species (including humans), potential differences in digestion and metabolism, as well as the unique pathophysiology of the same disease between species, can influence results. Considered lowest in value in evaluating potential clinical value of a dietary supplement are *in vitro* studies.

Assessment of Commercial Source

The regulatory category under which the commercial supplement is marketed may offer valuable insight to the veterinarian. An animal product labeled as a dietary supplement under the provisions of DSHEA (e.g., "Supplement Facts" box, "not evaluated by FDA" disclaimer) most likely has not been subject to scrutiny by CVM or state feed control officials so its compliance with applicable law can be questioned. However, notwithstanding some efforts by both the government and segments of the industry to market products as "unapproved drugs of low regulatory priority," many dietary supplements for animal use are labeled and offered as "food." Such products should meet CVM and AAFCO labeling requirements for animal feed. Indications that a label meets those requirements include an ingredient list wherein all ingredients are listed in descending order of predominance by weight, regardless of claimed functionality. Labels will also bear a "guaranteed analysis," including declarations of minimum percentages of crude protein and crude fat (where applicable), maximum percentages of crude fiber (where applicable), and moisture, followed by minimum amounts of each nutrient or other substance it purports to contain. For dog and cat products, guarantees for substances that are not recognized dietary essential nutrients for the intended species must include a disclaimer: "Not recognized as an essential nutrient by the AAFCO Dog (or Cat) Food Nutrient Profiles." Labels of products sold as animal feeds should not bear drug claims.

Most states, particularly those who have adopted the AAFCO Model Bill and Regulations, require registration of products and/or licensure of companies distributing products in that state. In general, this requires submission of labels to the state feed control official for review prior to distribution. Unfortunately, most states do not publish an easily accessible list of products or companies deemed to be acceptable in that jurisdiction. The Oregon Department of Agriculture is an exception, and it does allow search for companies licensed in the state (http://www.oda.state.or.us/dbs/licenses/search.lasso?&division=commercial_feed). If a general list is not easily obtained, feed control officials may be willing to confirm whether a particular product or company has been approved by that state when asked by a veterinarian or other member of the public. Appropriate contacts for each state can be found in the AAFCO Official Publication (AAFCO 2007), or on the "members" list on its website (http://www.aafco.org).

Animal drugs (approved or unapproved), as well as "dosage form animal health products" under NASC guidance are labeled in a different format than feeds. "Active ingredients" are listed first, along with a declaration of quantity of the ingredient per defined unit. Following these the "inactive ingredients" are declared in nonquantitative terms.

The regulation of animal drugs is generally not within the authority of state feed control officials. However, some states also enforce "animal remedy" laws, which may require registration. The Oregon Department of

Agriculture maintains a searchable database of veterinary drug companies (http://www.oda.state.or.us/dbs/licenses/search.lasso?&division=vet_products). Unique to Oregon is the fact that any product, including a pet food or supplement, with "health" or "healthy" in its product name is registered as a veterinary drug, not a feed.

The practitioner may also have a choice between a supplement labeled expressly for animals and one for human consumption. Presumably, the former would be preferred, as it would be assumed to contain concentrations of the functional ingredient in amounts appropriate for the species. It may also be in a form more readily accepted by the animal (e.g., chewable pill or powder, appropriately flavored).

However, a particular supplement designed for animal consumption may not always be available on the market, or only in combination with other ingredients that may not be indicated or appropriate for that animal. Another point to consider is that human dietary supplements regulated under DSHEA, for all its limitations, are now subject to GMPs for dietary supplements in FDA regulations (http://www.fda.gov/bbs/topics/NEWS/2007/NEW01657.html). Although there are manufacturing standards developed for animal dietary supplements for members of NASC, it is voluntary for nonmembers, and in any case, may not be subject to enforcement by regulatory officials. The U.S. Pharmacopeia, an official public-standards-setting body for drugs in the United States, also has a program that verifies the identity, strength, purity, and quality of human dietary supplements and their ingredients.

Finally, the manufacturer's history and reputation should be considered when choosing a supplement for use in practice. Is the brand widely known? Is the company willing to answer questions? Does it freely provide technical information on its products, manufacturing controls, or other areas of concern? Have colleagues had experience with the product or company? The veterinarian should proceed only when comfortable with the answers.

Assessment of Outcomes

Assuming, after proper evaluation of a supplement, the practitioner proceeds to use the product on patients, careful observation of the response of animals, positively or negatively, to administration is paramount to the decision of whether or not to continue using it in other clinical cases. Ideally, the supplement, and only the supplement, would be the sole treatment, so that the effects of other modalities would not obscure or interfere with the observations. However, in a practical situation this is likely to be the exception rather than the norm.

Because clinical or adverse response to a dietary supplement may not be as speedy or apparent as that to an approved drug, a product may have to be used on multiple patients over an extended period before a valid assessment of the outcomes can be conducted. As a fundamental component of the practice of evidence-based medicine, procedures to appropriately record clinical outcomes for later evaluation is detailed elsewhere (Faunt et al. 2007). Briefly, computerized records are preferred, in that they allow for easier search and capture of relevant clinical outcome information. Consistent use of standardized nomenclature in records helps ensure that all sought data is found. Establishing "best practice" treatment protocols that are followed by everyone in the practice enables outcome data for all patients to be compared equally.

Once appropriate data on outcomes are collected, a systematic evaluation can be revealing. Obviously, finding evidence of clinical improvement in the majority of patients compared to similar treatment without the supplement suggests that continued use of the supplement may be warranted. Just as importantly, a pattern of adverse effects may be discerned by comparing outcomes of treatments with or without the supplement. Adverse effects may include direct toxic effects, allergic reactions, or interactions with other drugs or treatments (Ramey 2007). Indirect effects, i.e., the potential consequences of delaying or replacing known effective conventional treatments with dietary supplements, should also be considered. Table 5.1 highlights the steps for the evaluation of dietary supplements.

Table 5.1. Steps for Evaluation of Dietary Supplements

Step	Key Considerations
Assess need	Sound basis for use Reliable source of recommendation Accurate diagnosis
Assess supportive data	Manufacturer studies Literature search Ranking of study strengths
Assess commercial source	Regulatory status (food or drug?) Human vs. animal supplement Company history/reputation
Assess outcomes	Keep consistent, searchable records Periodically evaluate outcomes

Table 5.2. Sources of Information on Dietary Supplements

Websites	
Assoc. American Feed Control Officials	http://www.aafco.org
Center for Veterinary Medicine	http://www.fda.gov/cvm
Food and Drug Administration	http://www.fda.gov
National Animal Supplement Council	http://www.nasc.cc
NIH Office of Dietary Supplements	http://ods.od.nih.gov
U.S. Pharmacopeia	http://www.usp.org
Veterinary Watch	http://www.veterinarywatch.com
Online bibliographic databases	
IBIDS (NIH Office of Dietary Supplements)	http://grande.nal.usda.gov/ibids/
PubMed (National Library of Medicine/NIH)	http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed
AGRICOLA (National Agricultural Library)	http://agricola.nal.usda.gov/

Sources of Information/Help

As mentioned above, there are several online bibliographic databases that offer free access to search the scientific literature. More comprehensive databases (e.g., CAB Direct) are available with subscription. Table 5.2 highlights several online sources of information.

FDA's website offers a lot of information on DSHEA and dietary supplements for human consumption. Policies as they relate to animal products may also be found on the websites of CVM and AAFCO. The AAFCO site also lists contacts for feed control officials in the various states. In addition to other possible remedies, veterinarians should contact the appropriate agency to report any observed adverse effects stemming from use of a dietary supplement. Although designed for approved drugs, CVM does maintain an adverse event reporting program that may be helpful (http://www.fda.gov/cvm/adetoc.htm).

Veterinary colleagues can be a great resource. Members of the Veterinary Information Network (http://www.vin.com) or the American Academy of Veterinary Nutrition (http://www.aavn.org) have access to experts on these organizations' listservs to whom they can ask questions about indications, use, and sources of dietary supplements for use in clinical practice.

SUMMARY

- The law under which dietary supplements for human consumption are regulated does not apply to animal products. Animal products are still subject to law as "foods" or "drugs," however.
- Some animal supplement products on the market may not wholly comply with applicable law, and they may contain unapproved ingredients or may make unsubstantiated claims.
- The veterinarian needs to critically evaluate the data supporting the efficacy and safety of a dietary supplement, as well as information on its source, prior to use on patients.

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Using Pet Food Labels and Product Guides

6

Sean J. Delaney and Andrea J. Fascetti

Pet food packaging and supportive product brochures or guides can be useful to the veterinary practitioner assessing a food. The following chapter highlights the clinically useful information available from these materials.

"READING" A PET FOOD LABEL

Overview of Regulatory Oversight

Packaging is governed by several groups or bodies (see Chapter 5 for more insight into pet food regulatory bodies). At the highest level is the federal or national regulatory body such as the U.S. Food and Drug Administration (FDA) and U.S. Department of Agriculture (USDA) followed by more localized governance at the state level. In the United States, most of the regulation and enforcement of pet food labels comes at the state level with state feed control officials ensuring labels are in compliance with guidelines published in the then-current *Official Publication* of the Association of American Feed Control Officials (AAFCO), which is generally adopted by state legislatures as law. Therefore, most of the rules governing a pet food label in the United States, and in many countries that adopt or adapt AAFCO guidelines, can be found in AAFCO's annually published *Official Publication*; the reader is encouraged to purchase a copy if further insight into pet food labeling in the United States is desired. With the rest of this section on pet food labels, the rules that will be covered apply to those established by AAFCO. Readers in other countries are encouraged to contact their local government to identify the rules that apply to their particular region. The second part of this chapter on using product guides, as well as sections on common calculations or conversions, should still be of use to all readers regardless of geography.

Principal Display Panel or Front Display Panel

Inherently, all front-facing portions of pet food labels and packages attempt to communicate the nature of the product and how it should be used, as well as draw the attention of the consumer. From a regulatory perspective the main consumer-facing portion of the label must contain only three elements: the product name, the intended species, and the net quantity of product within the package. Other elements that might assist with the other goals of the label such as company or distributor name, endorsements, comparative statements, or product highlights and images are optional. However, anything appearing on the label must be both truthful and substantiated.

Product Name

The name of the product is strictly regulated, and a product that says it is 100% of something must be exclusively that ingredient. This type of product is rare and is almost without exception incomplete and unbalanced, as typically these products are all meat without any minerals or vitamins added. Products that have meat and just enough minerals and vitamins to be complete and balanced typically fall under the 95% rule. If the 95% rule is used, then all 95% of the ingredient listed must be from an animal; therefore, a food labeled as "95% lamb & rice" would not be allowed but "95% lamb & beef" would be. It is worth noting that a little over half of the weight of the fresh meat typically found in such canned foods is from water, which

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counts toward the total inclusion percentage. Most pet foods fall under the 25% rule, which states that at least 25% of the food must be made up of the indicated ingredients with the first listed ingredient having the greatest inclusion among the ingredients in the product's name. In addition, the product name must include a descriptor such as "dinner," "formula," "entrée," or "recipe." With this rule, "25%" does not need to appear on the packaging, unlike the "100% rule" and "95% rule" where the percentages must generally appear (i.e., higher percentages than 95% could be listed). With the 25% rule, plant-derived ingredients may be included in the name. Therefore, "lamb & rice dinner" could be used and would mean that at least 25% of the food is lamb and rice and that the lamb is either equal to or greater than the amount of rice in the food (equal as the company can choose which to list first if the inclusion amount is the same). There is also a "with" or "3% rule," which means that any food "with" a separately identified ingredient (outside of the ingredient declaration) must have at least 3% of the ingredient (unless followed by the term "flavor" as discussed below). Unlike the 25% and 95% rules, this is not an additive rule. Thus, if one says "with lamb and rice" there needs to be 3% lamb and 3% rice. This rule does not apply to added minerals, vitamins, and trace nutrients that may appear in support of a food that is stating that it is "natural" (e.g., saying "natural pet food with added vitamins, minerals, and trace nutrients" does not mean, nor is it required to mean, that the food has 3% vitamins, 3% minerals, and 3% trace nutrients). Finally the last rule is the flavor rule, which is the vaguest and simply means that the food contains a source of the flavor that is "detectable." Therefore, awareness of naming rules can help to better understand the potential inclusion levels of named or highlighted ingredients and explain why, for instance, a largely chicken and corn-based food could be named "lamb & rice dinner" or how a pet food company can afford to sell an inexpensive food "with Angus beef." Interestingly, unlike the term "natural" which is defined by AAFCO, other commonly used terms like "premium," "super premium," and "organic" ("organic" is defined by the USDA National Organic Program) are not defined by AAFCO. Other descriptors such as "light," "lite," "low calorie," "lean," and "low fat" are defined and have specific cutoffs as to energy density or fat content that foods must meet to use these terms unlike the "comparative" terms such as "less calories," "reduced calories," "less fat," and "reduced fat," which are only defined by the level found in the product that is being compared. Thus, one cannot easily tell the caloric or fat content of a food described with a comparative term.

Back Panel

The most useful information on a package is located on the "back panel," as this is where information about nutritional adequacy, ingredients, nutrient levels, the company's contact information, and feeding amounts can be found, as well as (at times) calorie content information.

Nutritional Adequacy

Nutritional adequacy statements indicate for which species and for what life stage the food is appropriate. The term "all life stages" means that the food can be fed to gestating or lactating females, growing animals, and adults.

Adequacy can be established in three ways. The first way is by computer formulation to a specific nutritional profile established by AAFCO. The second method is with a feeding trial or protocol where the specific food has been fed to animals in a controlled setting with monitoring following a defined protocol. The last method, which cannot be determined from the label, is via the "family product rule," which allows foods, that are similar in ingredients and that have been tested to match or exceed key nutrient levels of another food that has passed a feeding trial or protocol, to claim that the unfed "family member" food passed a feeding trial or protocol for the same life stage. If a food is not complete and balanced, it must be labeled as a treat, snack, or supplement, or state that it is for "intermittent and supplemental feeding only." Unfortunately, this statement is very short and often not easily seen and results in clinical cases of nutritional deficiencies in the authors' experience.

Ingredient Declaration

Ingredients used in a food must be listed on the packaging and in descending order of inclusion before any cooking or drying takes place. Therefore, the first ingredient listed must have the greatest mass of all the ingredients in the formula or recipe. At times, companies will make formulation choices based on the resulting order of the ingredient declaration. The most commonly employed technique to change the ingredient declaration order is referred to as "ingredient splitting." In this method, an ingredient that may be perceived by the consumer as less desirable (such as corn) is "fractionated" into different components such as corn, corn meal, or corn gluten, in part so that the individual inclusion levels are less than the more desirable animal protein source like chicken or chicken meal. At times, it will also be raised that a dried product like "chicken meal" will provide more chicken protein than chicken, given the higher moisture and often higher fat content of the fresh ingredient. This is typically true for equal inclusion levels but really is an argument about

marketing strategies as much as anything else. In addition to listing ingredients by predominance, ingredients must be defined by AAFCO or the FDA to be used and must be the generic name (i.e., no brand or trade names). Often the veterinary practitioner will be asked what certain ingredient terms mean like "by-product" or "meal." The reader is encouraged to purchase a copy of the AAFCO *Official Publication* (see www.aafco.org for purchasing information) for examples of "by-products" and "meal" as defined by the AAFCO (as of 2011):

> 9.14 **Poultry By-Products** must consist of nonrendered clean parts of carcasses of slaughtered poultry such as heads, feet, viscera, free from fecal content and foreign matter, except in such trace amounts as might occur unavoidably in good factory practice. If the product bears a name descriptive of its kind, the name must correspond thereto. (Proposed 1963, Adopted 1964, Amended 2000.)
>
> 9.71 **Poultry Meal** is the dry rendered product from a combination of clean flesh and skin with or without accompanying bone, derived from the parts of whole carcasses of poultry or a combination thereof, exclusive of feathers, heads, feet, and entrails. It shall be suitable for use in animal food. If it bears a name descriptive of its kind, it must correspond thereto. (Proposed 1988, Adopted 1992.)

Also, references "to the quality, nature, form, or other attributes of an ingredient shall be allowed when the designation is not false or misleading; [and] the ingredient imparts a distinctive characteristic to the pet food because it possesses that attribute; [and] a reference to quality or grade of the ingredient does not appear in the ingredient statement." Thus, one cannot say "USDA Choice beef" in the ingredient declaration or list.

Nutrient Levels or Guaranteed Analysis

The guaranteed analysis must provide minimal nutrient information as follows:

- minimum percentage of crude protein
- minimum percentage of crude fat
- maximum percentage of crude fat (if using "lean" or "low fat")
- maximum percentage of crude fiber
- maximum percentage of moisture

Other guarantees must follow in the order they appear in the AAFCO profile, and if not listed in the AAFCO profile, must have the disclaimer "not recognized as an essential nutrient by the AAFCO dog [or cat] food nutrient profiles." As the reader will note, ash and carbohydrate percentages are not required. The absence of at least one of these two nutrients makes calculating the calorie content of a food more challenging and less precise, as will be discussed later. All guarantees must be for a nutrient, although a frequent exception is for "direct fed microbials" or probiotics, which are currently required to have a guarantee but are not nutrients. Also, all guarantees must be either a minimum or maximum value as averages or ranges cannot be used. It should be highlighted that the values listed are minimums or maximums, and although they may closely match the actual amount in the food, there can be some significant discrepancies. Therefore, if a particular nutrient level is important, the company should be contacted to ascertain the average nutrient level. One can quickly determine likely nutrient level minimums based on the nutritional adequacy statement. If a food is formulated to meet a nutrient profile for a particular life stage, nutrient levels should be equal or greater than the nutrient profile's minimums and equal or less than the nutrient profile's maximums. Since a food can pass a feeding trial without meeting a nutrient profile's values, one cannot make assumptions on nutrient values of foods that meet nutritional adequacy via a feeding trial. This knowledge can be useful to explain why no complete and balanced over-the-counter food that has been formulated to meet an AAFCO nutrient profile is low enough in phosphorus for the management of renal disease, as no phosphorus minimum in the AAFCO profiles is low enough.

Company's Contact Information

The company must provide its mailing address, although a street address can be omitted if they are listed in a city directory or phone book. Unfortunately, a telephone number is not required but is very important in the authors' opinion, as it enables any information that is unclear or unavailable on a label to be asked directly.

Feeding Directions or Guidelines

Feeding guidelines must be provided on packaging and must include at least "feed (weight/unit of product) per (weight only) of dog (or cat)," along with the frequency of the feeding. The exception is for veterinary foods, which can state "use only as directed by your veterinarian." Surprisingly, the calorie content of a food based on the AAFCO guidelines is not a required component nor is the energy equation or requirement used.

Calorie Content

Unfortunately the calorie content on the food is not currently required by AAFCO. Therefore, it is not uncommon

for the practitioner to have no idea of what the calorie content is or, more importantly, what a patient's food intake is, based solely on the food label(s). Fortunately, the practitioner can perform some simply calculations to estimate the calorie content of a food.

Estimating Calorie Content

One can use the required guaranteed analysis values to determine a food's calorie content or energy density. Unfortunately, as mentioned earlier, companies are not required to provide an ash or carbohydrate level, and actual values can vary greatly from the minimum and maximum values provided. Thus, the value that is generated is only an estimate (it is also only an estimate if actual levels for protein, fat, and carbohydrate are known, given the variability of digestibility that can affect the amount of energy these three macronutrients provide).

Step 1: Estimate carbohydrate content (this step can be skipped if the carbohydrate percentage for the food is provided). By subtracting the crude protein minimum percentage (CP %), crude fat minimum percentage (CF %), crude fiber maximum percentage (Fib %), moisture maximum percentage (M %), and ash maximum percentage (A %; if not reported, estimate between 2% and 10% using higher values with dry, higher protein foods) from 100, one can estimate the percentage of carbohydrate (CHO %). Written as an equation:

$$\text{CHO \%} = 100 - (\text{CP \%} + \text{CF \%} + \text{Fib \%} + \text{M \%} + \text{A \%})$$

Step 2: Estimate the calories from the macronutrients. By multiplying standard energy conversion factors (see Chapter 2; the example uses the modified Atwater factors) by the percentages for the minimum crude protein, minimum crude fat, and calculated carbohydrate, one can estimate the amount of calories coming from protein, fat, and carbohydrate. Written as equations:

$$\text{Calories from protein} = \text{CP \%} \times 3.5 \text{ kcal/g}$$

$$\text{Calories from fat} = \text{CF \%} \times 8.5 \text{ kcal/g}$$

$$\text{Calories from carbohydrate} = \text{CHO \%} \times 3.5 \text{ kcal/g}$$

Step 3: Estimate the total calories. By adding the Calories from protein, fat, and carbohydrate, one can estimate the total Calories available in 100 g of food as fed. **The Calories are from 100 g, as the percentage used for the earlier calculation is the same as gram of macronutrient per 100 g food as fed.** If the amount per kilogram is desired, the result can be multiplied by 10 since 10 × 100 g = 1,000 g or 1 kg. Written as equations:

$$\text{Total Calories/100 g food} = \text{Calories from protein} + \text{Calories from fat} + \text{Calories from carbohydrate}$$

$$\text{Total Calories/kg food} = \text{Total Calories/100 g food} \times 10$$

A useful estimate for the amount of calories per 8-fl-oz cup is to assume this volume of food weighs 100 g; therefore, 1 cup of dry food is roughly equal to the "Total Calories/100 g food" value above.

CALORIC DISTRIBUTION CALCULATION

The best method to compare levels of protein, fat, and carbohydrate is based on caloric distribution, which is simply the percent of the total calories that come from the three macronutrients. This enables direct comparisons to be made without concerns about varying moisture or fiber levels, which can vary greatly and impact other units of comparison. To calculate the Calories from protein, fat, or carbohydrate as determined above, one divides one of these values by the total Calories per 100 g of food and multiples by 100. Written as equations:

$$\text{Percent Calories from protein} = (\text{Calories from protein/total Calories per 100 g food}) \times 100$$

$$\text{Percent Calories from fat} = (\text{Calories from fat/total Calories per 100 g food}) \times 100$$

$$\text{Percent Calories from carbohydrate} = (\text{Calories from carbohydrate/total Calories per 100 g food}) \times 100$$

The three resulting values are referred to as the caloric distribution. These values are most useful for comparing and determining if a food is truly lower or higher in a particular macronutrient. Given their utility, they are provided in the product guides provided by manufacturers of veterinary therapeutic foods.

USING PRODUCT BROCHURES AND GUIDES

Product brochures and product guides can be an excellent repository of useful information about foods. They generally provide all the key nutritional information found on packaging, such as the ingredient list and guaranteed analysis (but generally not the nutritional adequacy statement) as well as available sizes and suggested uses along with highlighting features and benefits. For veterinary product guides, indications and contraindications are typically provided as are caloric distributions as well as key nutrients in units beyond those on an as-fed basis. Typically, the nutrients are provided in these guides on both a dry-matter basis and a per-100 kcal or per-1,000 kcal or Mcal (energy)

basis. Generally, comparing nutrient levels on a dry matter basis has fallen out of favor with the preference to compare nutrients on a per-unit of energy basis. If calorie density is not taken into account, one can derive the wrong conclusions when comparing foods based on dry matter alone. Therefore, it is important to be able to calculate the amount of nutrient on a per-unit of energy basis. This can be best illustrated with the example in Box 6.1.

BOX 6.1

If one has a food with 3,000 kcal/kg as fed, 10% moisture, and 1% calcium, and a second food with 4,750 kcal/kg as fed, 10% moisture, and 1.1% calcium, the practitioner may be led to believe that their patient is getting more calcium from the second food as it has more calcium on a dry matter (DM) basis: 1.11% DM versus 1.22% [(1/(1 − 0.1) = 1.11% dry matter versus the second food with 1.1/(1 − 0.1) = 1.22%]. However, patients eat to meet their energy requirement (see Chapter 2); therefore, let's say the patient consumes 1,000 kcal/day. On the first food, the patient will get 3.3 g calcium per day:

$$1\% \times 1{,}000 \text{ g/kg} = 10 \text{ g calcium/kg}$$

$$10 \text{ g}/3{,}000 \text{ kcal/kg} = 0.0033 \text{ g/kcal}$$

$$0.0033 \times 1000 = 3.3 \text{ g}/1{,}000 \text{ kcal or } 3.3 \text{ g/Mcal or } 3.3 \text{ mg/kcal}$$

$$1{,}000 \text{ kcal} \times 3.3 \text{ mg/kcal} = 3{,}300 \text{ mg/day or } 3.3 \text{ g/day}$$

And on the second food, the patient will get 2.316 g calcium per day:

$$1.1\% \times 1{,}000 \text{ g/kg} = 11 \text{ g calcium/kg}$$

$$11 \text{ g}/4{,}750 \text{ kcal/kg} = 0.0023$$

$$0.0023 \times 1{,}000 = 2.3 \text{ g}/1{,}000 \text{ kcal or } 2.3 \text{ g/Mcal or } 2.3 \text{ mg/kcal}$$

$$1{,}000 \text{ kcal} \times 2.3 \text{ mg/kcal} = 2{,}300 \text{ mg/day or } 2.3 \text{ g/day}$$

This means that the patient eating the second food will consume 30% less calcium than on the first food. If the practitioner had just looked at the information on a dry matter basis, they would have thought that the patient was getting less calcium with the first food.

Converting Nutrient Levels to a Dry Matter Basis

To calculate a food's content on a dry matter basis, the percent moisture is subtracted from 100 and then divided by 100, and the resulting value is used to divide the "as-fed" value of interest (units are not important as they do not change with the conversion) to get the dry matter value. For example, for a food with 25% protein as fed and 10% moisture, the equation and the result would be:

$$25\% \text{ protein as fed}/[(100 - 10)/100] = 25/0.9 = 27.78\% \text{ protein dry matter}$$

Since most dry foods have ~10% moisture and canned foods ~75% moisture, one can simply divide by 0.9 or 0.25 for dry and canned foods, respectively, to convert to a rough estimate of the dry matter value when the moisture level is unknown but the format of the food is.

Converting Nutrient Levels to an Energy Basis

To convert or calculate the amount of a nutrient on an energy basis (typically written as "mass/1,000 kcal" or "mass/Mcal"), one needs to know the kcal/kg amount (see above for how to estimate this value from the label if unavailable). If the nutrient is provided as a percentage it will need to be first converted to a mass (gram is the easiest and the most common unit of mass used; other units such as milligrams (mg), micrograms (mcg), and International Units (IU) do not need to be converted as the starting unit will be kept) per kilogram of food on an as-fed basis. For example, if the food has 2% calcium, one can divide the percentage by 100 and then multiply the result by 1,000 to get the grams of calcium per kilogram of food as fed. Thus, (2/100) × 1,000 = 20 g calcium/kg of food as fed. With the kcal/kg as-fed value and the mass of nutrient per kg as fed, one simply divides the nutrient mass by the kcal/kg value and multiplies the result by 1,000. Thus the equation for a food with 3,000 kcal/kg as fed and 20 g calcium/kg is:

$$(20 \text{ g calcium}/3{,}000 \text{ kcal/kg food as fed}) \times 1{,}000 = 6.67 \text{ g calcium per Mcal}$$

Converting to Other Units

Occasionally, one will encounter other units, and the reader is encouraged to use the method whereby unwanted units are canceled by using known conversion factors. For example, if one wishes to convert 50 IU of vitamin A to micrograms (mcg) of retinol, one can perform this conversion by knowing that 1 IU vitamin A = 0.3 mcg retinol and then canceling units by putting like units opposite like units in the numerator or denominator of equations as in the following:

$$50\ \text{IU vitamin A} \times (0.3\ \text{mcg retinol}/1\ \text{IU vitamin A}) = 15/1 = 15\ \text{mcg retinol}$$

In the equation above, note how one IU value is a numerator (i.e., 50 IU vitamin A = 50 IU vitamin A/1, thus the "50 IU" is in the numerator) and one IU value is a denominator (i.e., "1 IU"). This enables the units to be canceled as the numerator and denominators are multiplied by each other and the numerator product is divided by the denominator product. Other encountered conversions are 40 IU vitamin D3 = 1 mcg cholecalciferol; 1 IU vitamin E = 1 mg all-*rac*-alpha-tocopheryl acetate; 1 kg = 1,000 g; 1 g = 1,000 mg, and 1 mg = 1,000 mcg. As noted elsewhere in the text (see Chapter 3) 1 Calorie = 4.185 kiloJoule.

Product Guide Recommendations for Conditions and Diseases

With the "tools" described above to determine a food's caloric distribution and nutrient amounts per megacalorie, the reader should be better equipped to make comparisons among foods. These tools can be best employed to compare and contrast approaches and recommendations for the management and treatment of different conditions and diseases as found in veterinary product guides and online (websites can often be more up to date as formulation changes may occur more frequently than the release of brochure/guide reprints). One will find that for many conditions and diseases there is a general agreement about the best strategies for nutritional management. However, the reader is strongly encouraged to confirm that these general recommendations apply to the specific needs of particular patients. For others there can be varying philosophies, and the reader is encouraged to use the remainder of this text to aid them in exploring these approaches and recognizing when and where product guide recommendations may vary or differ.

SUMMARY

- Packaging and product guides provide required and at times useful nutritional information about foods.
- The information provided can be used to determine a food's energy density and caloric distribution as well as nutrient amounts on a dry matter and energy basis.
- Nutrient amounts, ingredient lists, feeding guidelines, and product guide recommendations can all be useful in selecting the best food for patients.

RECOMMENDED RESOURCES

Official Publication of the Association American Feed Control Officials, available for purchase at http://www.aafco.org

U.S. Food and Drug Administration, Center for Veterinary Medicine Websites (as of January 2011):
http://www.fda.gov/AnimalVeterinary/default.htm
http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/PetFood/default.htm

Feeding the Healthy Dog and Cat

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INTRODUCTION

Both dogs and cats are members of the biological order Carnivora. Scientific observation and research support that differences in their metabolism and nutritional requirements exist. The differences in nutritional requirements likely correlate with the evolution of these two species. Nutritionally and metabolically, dogs and other members of Cannidea are generally considered omnivores, whereas cats and other members of the family Felidea are regarded as carnivores. However, there exist nutritional and metabolic examples that are not consistent with the view that the cat is a strict carnivore and the dog is simply an omnivore.

The only member of the family Felidea whose nutritional requirements have been studied extensively is the domestic cat (*Felis catus*). Scientific research has shown that cats have obligatory requirements for nutrients that are not essential for many other mammals. The high protein requirement of cats is due to their high requirement for nitrogen. This appears to be because cats have a limited ability to control the activity of their aminotransferases and urea cycle enzymes (Rogers, Morris et al. 1977; Green et al. 2008). Conversely, cats are able to control the activity of enzymes in the first irreversible step of essential amino acid degradation to some extent, explaining why they do not have a high requirement for essential amino acids (Rogers and Morris 1980). The lack of downregulatory control over aminotransferases and urea cycle enzymes renders cats immediately able to metabolize and use amino acids for gluconeogenesis and as an energy source. Additional benefits of this ability are realized in times of starvation; carnivores are better able to immediately maintain blood glucose concentrations compared to omnivorous species (Morris 2002).

There are five other nutrients, considered essential in feline diets, that are not recognized as essential in most other species due to the low activities of enzymes in their synthetic pathways. Two of these nutrients are the amino acids arginine and taurine. The low activities of ornithine aminotransferase and pyrroline-5-carboxylate result in the minimal production of citrulline in the gastrointestinal tract (Costello et al. 1980; Rogers and Phang 1985). As a result, the cat is completely dependent upon dietary arginine to meet its needs for this amino acid. The endogenous synthesis of taurine is limited by the low activities of cysteine dioxygenase and cysteine sulfinic acid decarboxylase (Park et al. 1999). The low activity of these enzymes in the synthetic pathway, coupled with the low affinity of N acyltransferase for glycine for bile acid synthesis, results in the depletion of body taurine stores. The remaining three nutrients are niacin, vitamin A, and vitamin D. The cat has a dietary requirement for niacin and vitamin D because of the high activity of the enzymes picolinic carboxylase (Sudadolnik et al. 1957; Ikeda et al. 1965) and 7-dehydrocholesterol-Δ^7- reductase (Morris 1999), respectively, that result in the degradation of precursors for their synthesis. Vitamin A must be supplied preformed in the diet presumably because cats lack or have reduced activity of the enzyme β,β-carotene 15, 15'–dioxygenase, needed to cleave β-carotene (NRC 2006).

Consistent with their classification as obligate carnivores, cats have a reduced number of carbohydrate metabolizing enzymes compared to omnivores. Cats lack

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glucokinase in their livers (Washizu et al. 1999). However, in contrast to certain others carnivores, and not at all consistent with the cat being a strict carnivore, cats can efficiently digest cooked starch (Morris, Trudell et al. 1977; Kienzle 1993).

Nutritionally and metabolically, many consider the dog an omnivore. However, there are nutritional and metabolic characteristics that dogs share with the cat. One veterinary nutritionist (D. Kronfeld) has suggested the term "adaptive carnivore" when referring to the dog. In contrast to the cat, and similar to other omnivores, the dog has the ability to make taurine from the sulfur amino acid precursors methionine and cysteine (Hayes 1988), as well as vitamin A from β-carotene (Turner 1934). However, unlike many other omnivores and more like the cat, the dog conjugates bile acids only with taurine (Haslewood 1964) and cannot make vitamin D, an animal product (Hazewinkel et al. 1987; How et al. 1994; NRC 2006). Like cats, dogs require a source of dietary arginine to maintain nitrogen balance in adults and puppies (Ha et al. 1978; Czarnecki and Baker 1984). The dog's requirement for arginine is less than that of the cat but greater than that of the rat (NRC 2006), positioning it between carnivores and other omnivores nutritionally.

Over time, evolution rendered some of the metabolic pathways and enzymes present in omnivores redundant in the cat. These pressures likely resulted in changes in biochemical pathways and nutritional requirements more suited to the cat's metabolism (Morris 2002). Although nutritional requirements of the cat differ from that of the dog, scientific findings and observations are not fully consistent with the cat being a strict carnivore and the dog a simple omnivore.

FEEDING THE HEALTHY DOG AND CAT

Healthy animals normally eat sufficient food to satisfy their energy requirements. It is one of the jobs of the nutritionist to ensure that all other nutrient needs have been met when animals stop eating because they have met their energy needs. The greatest metabolic demands occur during growth, gestation, and lactation, and this is when a marginal diet is most likely to result in nutritional problems. The majority of commercial pet foods are formulated to ensure adequate intake of all required nutrients based on energy intake as long as consideration is given to the manufacturer's life-stage recommendation.

How Much to Feed

Ideally, the amount of food to feed an animal should be determined based on a diet history (Fig. 7.1). Diet history forms should be obtained and updated for every patient in your practice at every visit. Information that should be included in every diet history form includes, the specific product name, form (i.e., dry, canned, or semi-moist), and manufacturer of the pet's diet, quantitative data on how much the pet is consuming daily, details regarding names and amounts of snacks and treats, information about who feeds the pet, and the setting in which the pet consumes its food. It is also a good idea to ask how the food is stored and more details regarding additional animals in the household and potential access to other food sources. In instances where owners are home-preparing the pet's meals, detailed information on the ingredients and supplements as well as preparation methods should be requested and entered into the record. When the animal is in an ideal body condition, weight stable, and otherwise healthy, these authors recommend feeding the amount of food the animal is currently consuming provided an accurate and detailed diet history is available.

If the exact number of calories to feed is difficult to determine with certainty, in some cases it can be approximated. Although many animals are fed free choice, owners should still be able to provide an estimate of how much food the animal receives daily. The estimated number of calories currently consumed can then be compared to the required maintenance requirements based on calculation. This information should be considered in light of the animal's body condition score and any history of recent weight loss or gain when arriving at a final decision regarding the appropriate amount of calories to feed.

Determining the amount of calories to feed becomes more difficult if a diet history is unavailable. Many pet foods provide guidelines on the product label, and these can be used as a starting point. It is important to understand that these guidelines are limited, however, due to the variation of efficiency of food utilization among animals and individual differences in physical activity, metabolism, body condition, and environment. Controlled studies have demonstrated that energy requirements may vary significantly among similar animals housed in similar conditions (NRC 2006). Therefore, the calculated food dosage should be considered as a starting point that will most likely have to be adjusted. The authors recommend determining the animal's maintenance energy requirement (MER) by using the resting energy requirement (RER) equation and then multiplying by the factor for the appropriate life stage rather than using the single MER equation. In many cases the single MER equation overestimates the animal's energy needs (Lewis and Morris 1987a). However, it is imperative to remember that the calculated amount to

DIET HISTORY FORM

Provided by Veterinary TECHNICIAN

Content courtesy of the Nutrition Support Center University of California–Davis Veterinary Medical Teaching Hospital

UCDAVIS UNIVERSITY OF CALIFORNIA

TO BE COMPLETED BY CLIENT

Client Information

Name:_____ Date: _____

Address: _____

City:_____ State:_____ Zip:_____

Telephone (home):_____ (other): _____

Email address: _____

Patient Information

Name:_____ Species:_____ Breed:_____

Age:_____ Sex: ❑ Male ❑ Female ❑ Neutered/spayed

1. Where is your pet housed? ❑ Indoors ❑ Outdoors ❑ Both ❑ Outside mainly for walks or exercise

2. Please describe your pet's activity level (i.e., type, duration, frequency): _____

_____

_____

3. Do you have other pets? ❑ Yes ❑ No If so, please list: _____

_____

4. Is your pet fed in the presence of other animals? ❑ Yes ❑ No If yes, please describe: _____

_____

5. Is food left out for your pet during the day or taken away after the meal? _____

_____

6. Does your pet have access to other, unmonitored food sources (e.g., treats fed by neighbor, food left for outdoor cats)?

❑ Yes ❑ No If yes, please describe: _____

_____

_____

7. Who typically feeds your pet? _____

Fig. 7.1. Diet history form (used with permission from *Veterinary Technician Magazine,* January 2008).

DIET HISTORY FORM

8. How do you store your pet's food? _____

_____

9. Please list your pet's current and past medical problems, if any, and whether they have been resolved:

_____

_____

10. Please list all the medications your pet is currently receiving and any that have been administered over the past 3 months:

_____

_____

11. Please indicate whether your pet has experienced any of the following problems before today's visit:

Recent involuntary or unintended ❑ Weight gain ❑ Weight loss How many pounds? _____

Over what time period? _____

❑ Vomiting _____ times/day _____ times/week ❑ Diarrhea _____ times/day _____ times/week

12. Have you observed changes in any of the following?

❑ Urination ❑ Drinking What was the specific change? _____

Since when? _____

❑ Defecation What was the specific change? _____

Since when? _____

❑ Appetite What was the specific change? _____

Since when? _____

13. Does your pet have any of the following? ❑ Allergies ❑ Difficulty chewing ❑ Difficulty swallowing

If so, please describe: _____

Current and Previous Diets and Supplements

Below, please list the brand or product names (if applicable) and amounts of all foods, snacks, and treats your pet *currently* eats. This description should provide enough detail so that anyone could go to the store and purchase the same food. It should include human foods given as treats or at the table. Three examples are given in italics.

Brand/Product/Food	Form	Amount Fed per Meal	No. of Meals	Fed Since
EXAMPLES:				
Brand X Dog Food	*Dry*	*1½ cups*	*Twice a day*	*5/00*
Brand A Dog Treats	*Treats*	*1/day*	*—*	*8/01*

Fig. 7.1. *Continued*

DIET HISTORY FORM

Boneless chicken (white meat)	*Boiled*	*2 ounces*	*3 times a week*	*6/98*

Please list other diets your pet has received in the past, indicating the approximate time period when they were fed. Two examples are given in italics.

Brand/Product/Food	Form	Amount Fed per Meal	Time Period Fed	No. of Meals	Reason Stopped
EXAMPLES:					
Brand Y Puppy Food	*Can*	*6½ ounces*	*6/99 to 12/99*	*Twice a day*	*Became an adult*
Brand Z Puppy Food	*Dry*	*1½ cups*	*6/99 to 3/00*	*Twice a day*	*Became an adult*

Please list the name of each additional supplement your pet receives, and indicate how much and how often your pet receives it (i.e., herbal product, fatty acid, vitamin or mineral supplement):

Patient Dietary Preferences

Please complete this section *only* if a home-cooked diet formulation is being requested or may be needed. If the diet formulation is needed due to an adverse reaction to certain foods, please provide protein and carbohydrate options that are both *palatable* and *tolerated* by your pet. This will need to be determined before submitting this consult.

Protein Sources

- ❑ Beef
- ❑ Chicken
- ❑ Cottage Cheese
- ❑ Crab
- ❑ Egg
- ❑ Lamb
- ❑ Pork
- ❑ Salmon
- ❑ Tofu
- ❑ Tuna
- ❑ Turkey
- ❑ Whitefish
- Other _____
- Other _____

Carbohydrate Sources

- ❑ Barley
- ❑ Millet
- ❑ Oatmeal
- ❑ Pasta, Spaghetti
- ❑ Peas, Green
- ❑ Potato, Sweet
- ❑ Potato, White
- ❑ Quinoa
- ❑ Rice, Brown
- ❑ Rice, White
- ❑ Tapioca
- Other _____
- Other _____
- Other _____

Fig. 7.1. *Continued*

feed is only an educated guess (or a starting point) and that this amount may vary by as much as 50%, particularly for dogs (NRC 2006). The animal's weight and body condition score should be monitored frequently and the caloric intake adjusted accordingly.

WHEN AND HOW TO FEED

There are basically three types of feeding regimens that humans use to feed their dog or cat. It is also not uncommon to see more than one of these in the same animal.

Free-Choice (*ad libitum*, self-feeding)

This approach ensures that there is a surplus of food available at all times, and it is often the method of choice for the queen or bitch during lactation. *Ad libitum* feeding relies upon the animal regulating its daily caloric intake. This type of feeding allows cats to consume small multiple meals throughout the day, closely mimicking their natural feeding behavior (Kane et al. 1981). This method of feeding provides the least amount of work on behalf of the owner. Free-choice feeding may be advantageous for animals who tend to consume small multiple meals, or for picky or slow eaters that can't consume enough calories in one meal. Furthermore, there may be an advantage concerning energy balance due to meal-induced energy loss. In a kennel situation, this method helps to minimize the noise associated with feeding and may relieve boredom. Free-choice feeding helps to ensure that the subordinate animals in multiple pet households have the opportunity to eat. The disadvantages associated with an *ad libitum* feeding schedule include the likelihood of overlooking medical problems, anorexia, or the denial of food to subordinate animals when food intake is not closely monitored. Most importantly, this style of feeding increases the probability an animal will become overweight. It has been suggested that 30–40% of dogs and cats will overeat if food is available at all times (NRC 2006). Dry food is the only type of pet food that can be fed in this manner. Canned food, some semi-moist food, and dry food combined with water should not be left out in the environment for extended periods of time.

Time-Restricted Meal Feeding

Similar to the free-choice style of feeding, this method relies upon the animal's ability to regulate its daily caloric intake. At meal time, a surplus of food is given, and the pet is allowed to eat for a set period of time. This form of feeding is most applicable to dogs but not practical for cats. Most dogs will learn to consume their energy requirements in a 5- to 15-minute time period. Proponents of this manner of feeding recommend a twice a day schedule to minimize begging. The major advantages of this method are that it does not require much effort on behalf of the owner and may be used with any type of pet food. It also permits some monitoring of the dog's food intake. This form of feeding may not be appropriate for fastidious animals that are not able to consume enough food in the allotted time period to meet their caloric needs. Meal feeding may also encourage gluttony and aerophagia.

Portion-Controlled Feeding

With portion-controlled feeding the dog or cat is given a specific amount of food, often divided into two meals per day. This method of feeding is considered by many experts to be the best approach for both dogs and cats in all life stages. The advantage of this method is that it allows the owner to carefully monitor their pet's food intake. This may ultimately result in a lower probability of the development of obesity. This method of feeding also alerts an owner much sooner to any medical problems or anorexia. The biggest disadvantage of portion-controlled feeding is that it requires more of a time commitment and effort on behalf of the owner.

Snacks and Treats

A recent study reported that 56.8% of dogs and 26.1% of cats receive a treat at least once daily (Laflamme, Abood et al. 2008). Offering a treat or sharing food with one's pet is an important part of the human–animal bond and should be included in a diet plan for every patient. The authors recommend that the energy intake from snacks or treats not exceed 10% of the animal's total daily calories. Intakes above this amount increase the risk of creating a nutritional imbalance in the animal's diet. Some commercial treats are formulated to support various life stages, so the utilization of such products will reduce that risk. Regardless of which approach to treats an owner chooses, they should be advised to avoid treats that are extremely high in fat. High-fat treats may incite gastrointestinal problems or pancreatitis in susceptible populations and are very calorie dense, thereby limiting the number or amount that can be fed daily. Human foods can also be used as treats. The United States Department of Agriculture's (USDA) National Nutrient Database for Standard Reference (http://www.nal.usda.gov/fnic/foodcomp/search/) is a very useful resource to determine the calorie content of human foods.

WHAT TO FEED

"What is the best diet for my pet?" is one question the authors are often asked. The answer is: "There is no one

diet that is best for every cat or dog. Cats and dogs are individuals, and the best diet will vary from animal to animal." That being said, it is helpful to clients to provide some guidelines for choosing a diet for their healthy animal and even more helpful if one can give them a few specific recommendations. When considering the appropriate response to this question, it is important that the clinician consider three factors: (1) the animal in question, (2) the variety of external factors that may influence how and what the animal is fed, and finally (3) the product itself.

There are many factors related to the animal that will influence your suggestions. One must consider not only the animal's signalment (i.e., age, species, breed, and sexual status) but its body condition, activity levels, and food or texture preferences. It is also helpful to know if the animal is a normal or finicky eater.

External factors can have a strong influence on your final dietary recommendations for the pet. Knowing the owner's budget can help narrow your recommendations to products that meet their price range. The diet and how the animal is fed may be influenced by its environment, which includes, but is not limited to, the number and type of the animals in the household, where the animal is housed (i.e, indoors versus outdoors), the human inhabitants of the house (i.e, a household with small children, elderly individuals, or adults only), and the feeding philosophies of the owner. Some owners follow a particular dietary philosophy for themselves (e.g., vegetarian, organic, locally sourced food, etc.) and want to apply that approach to their animals as well.

After assessing your patient and reviewing the external factors in that animal's environment, consideration needs to be given to the product itself. It is important to select a diet that supports the life stage of the patient that one is feeding and a lean body condition when fed an appropriate amount. The authors recommend feeding foods produced by larger manufacturers, so that if there is a problem with a particular diet it will likely be detected sooner. Strong consideration should be given to companies that employ animal nutritionists and support research in an effort to continually improve foods and the knowledge about dog and cat nutrition. When making specific recommendations, the authors prefer foods that have undergone and passed feeding trials in accordance with the guidelines of the Association of American Feed Control Officials (AAFCO) (see Chapter 6). It is unfortunate that the current court of public opinion seems to view such feeding trials negatively and as generally yielding little useful data. This opinion is often expressed by well-intentioned individuals with little understanding of the process or dog and cat nutrition. While such trials do have limitations with respect to catching long-term nutritional problems, all life stage feeding trials can pick up concerns before a food is marketed (personal communication, Q.R. Rogers and A.J. Fascetti). Many critics are also unaware of the fact that even though a product states it is formulated to meet an AAFCO nutrient profile that does not mean it will pass a feeding trial for the life stage it is designed to support. Nonetheless, even many reputable companies are no longer conducting feeding trials in an effort to appease their customers, so it makes it harder to say every food should undergo a feeding trial in order to recommend it to a client. The authors are comfortable recommending foods that have not undergone feeding trials when they are produced by larger companies that have a long history of making foods and a good working knowledge of their ingredients. While not necessarily conducting an official AAFCO trial, many of these companies still have current knowledge on how their products perform by continually feeding their diets to dogs and cats in a controlled setting. There is less confidence in foods from newer or smaller companies that have not conducted any feeding trials and may not have any historical data on how their formulations or ingredients perform, and/or they may not have maintained animals for years on their foods. Special concern is warranted with regard to products that employ newer feeding approaches, such as raw food, especially when largely unsupplemented with essential minerals and vitamins. Data from the controlled feeding of these diets are virtually nonexistent, so pets eating these foods are in essence the test animals if the manufacturer has not tested the food prior to release into the market.

FEEDING GUIDELINES FOR DIFFERENT LIFE STAGES

Gestation and Lactation

For mammals, the period of pregnancy puts a significant nutritional demand on both the dam and the fetus. Both mother and offspring are in a positive energy and nitrogen balance. Given the nutritional demands of this life stage, it is important that the diet be one that supplies all the energy and nutrients needed to meet the maintenance requirements of the queen or bitch in addition to supplying all the energy and nutrients required to support fetal growth and development and milk demands during lactation (Wills 1996).

Cats

Queens that are significantly under- or overweight should not be bred until their body condition is closer to ideal (5

out of 9 on a 9-point scale). Malnourished queens are more likely to not conceive or have kittens that are underweight and perform poorly during lactation (personal communication, A.J. Fascetti). It has been reported that obese cats have a higher incidence of dystocia (Lawler and Monti 1984).

Weight gain in cats is unlike other mammals such as humans and dogs, where most weight is gained in late pregnancy (Wills 1996). Cats, like pigs, show a different pattern characterized by a linear gain throughout pregnancy that is independent of the number of fetuses (Loveridge 1986; Wichert et al. 2009). Energy intake parallels this linear weight gain. It has been estimated that energy requirements increase approximately 25–50% above maintenance to between 90 and 100 kcal/kg body weight/day (Loveridge and Rivers 1989).

Just prior to and immediately following parturition, food intake is reduced, but quickly increases driven by the need for energy to meet the demands of lactation (Legrand-Defretin and Munday 1993). Following parturition, approximately 40% of the weight gained during gestation is lost, and by the time the kittens are weaned from the queen she should have returned to her pre-breeding weight (Loveridge and Rivers 1989). However, a recent study found that most queens were heavier than their breeding weight 2 weeks following weaning (Wichert et al. 2009). The retention of some weight allows the queen to maintain a body fat reserve to use as energy during lactation (Wills 1996). This may be because it is difficult for the queen to consume enough energy through her diet alone to meet this demand.

Lactation is considered to be the most demanding life stage with regard to energy and nutrient needs. It has been suggested that the actual energy and protein requirements of lactating queens may in fact exceed current NRC recommendations (Wichert et al. 2009). During lactation, energy demands peak at about the seventh week, although peak milk production typically occurs at week 3 (Munday and Earle 1991). This discrepancy occurs because energy intake at week 7 not only includes the calories consumed by the queen but also those eaten by the kittens that are consuming a portion of their intake from the queen's diet at this time (Munday and Earle 1991).

Because cats begin to increase their energy intake shortly after conception, it is recommended that queens be fed a diet designed to support gestation and lactation prior to breeding and continue with this food until weaning. The diet should be concentrated in terms of its energy density, and be highly digestible and palatable. Such a diet will assist in meeting the queen's high energy demands without volume restriction. To further assist with this goal, queens should be fed free choice throughout these two life stages. Following the weaning of their kittens, queens can be returned to their normal maintenance ration.

Dogs

Like cats, it has been recommended that dogs be fed a complete and balanced diet and be in an ideal body condition prior to breeding. While supportive studies are lacking, one could speculate that malnourished bitches will have lower conception rates and perform poorly during lactation. It has been reported that puppies born to malnourished dogs have reduced birth weights, are prone to hypoglycemia, and have poor survival rates (Schroeder et al. 1994). Bitches that are obese prior to breeding have lower ovulation rates, smaller litter sizes, and perform poorly during lactation (Bebiak et al. 1987; Debraekeleer et al. 2010).

Unlike cats, the bitch's energy requirements will not increase until the last third of gestation. In general the average bitch will gain anywhere from 15–25% of her pre-breeding weight prior to whelping (Legrand-Defretin and Munday 1993). Energy requirements for gestation peak anywhere between 30% and 60% of the pre-breeding requirements depending upon the litter size (Romsos et al. 1981; Debraekeleer et al. 2010). Energy requirements continue to increase following whelping and into lactation, peaking at approximately 3 to 5 weeks. At this point, energy requirements can fall between two and four times the adult maintenance requirement (Ontko and Phillips 1958; Legrand-Defretin and Munday 1993).

It is recommended that all breeding bitches be at an ideal body condition prior to conception. A diet designed to support the life stages of gestation and lactation should be selected and started prior to breeding and fed to maintain an ideal body condition. As the need for extra energy and nutrients is relatively small, a gradual increase in amount of energy offered can be started during the second half of gestation. Every animal should be fed on an individual basis, but one suggestion is to consider beginning to increase the amount of calories offered by 10–15% each week around the fifth week of gestation until whelping (Wills 1996). This approach results in an overall increase of approximately 40–60% compared to the food intake at the time of breeding. In many cases offering two meals per day during the last few weeks of gestation is sufficient for the dam to meet her energy needs. However, some giant breed dogs and bitches with large litters may need to be fed free choice due to volume limitations (Mosier 1977; Debraekeleer et al. 2010). During lactation, with the exception of when a bitch only has one or two surviving puppies, most dogs should be fed free choice or small, multiple meals throughout the day to allow them to meet

their energy needs and produce adequate milk for their offspring. The amount of calories offered can be reduced as the weaning process is started; this helps reduce the amount of milk the bitch is producing. Once weaning has been completed, the bitch should be fed the same amount of calories as her pre-breeding intake.

There is some controversy regarding the need for carbohydrates in diets fed to bitches during gestation and lactation. Romsos et al. (1981) reported smaller litter sizes in Beagles fed a diet containing 26% of the calories from protein and 74% from fat. A second study fed a carbohydrate-free diet containing 42% of the calories from protein and 58% from fat (Kienzle, Meyer et al. 1985). In that study, litter sizes, birth weights, and puppy survival rates were comparable to control dogs consuming a diet with carbohydrates. These data indicate that although pregnant and lactating bitches do not require a dietary source of carbohydrate, they have an increased protein requirement when a carbohydrate-free diet is fed (NRC 2006). That being said, there are some data to support that the lactose content of the milk is higher when a diet containing some carbohydrate is fed (Kienzle, Meyer et al. 1985). The recommendations from that study are that diets for lactation provide at least 10–20% of the energy from digestible carbohydrates (Kienzle, Meyer et al. 1985).

Supplementation During Gestation and Lactation

Some breeders regularly supplement their bitch's or queen's diet with calcium or calcium-containing foods such as cottage cheese throughout gestation or lactation. This stems from the theory that the added minerals will ensure healthy fetal development, prevent eclampsia, and aid in milk production. This practice is not necessary as long as the dam is consuming a commercial ration designed to support gestation/lactation. In fact, some experts feel that excess supplements during pregnancy may adversely affect skeletal development, result in fetal deformities or problems during growth, and actually increase the likelihood of eclampsia (Linde-Forsberg 2010). The higher calcium needs that result during gestation and lactation are met by increasing energy consumption from a diet that is nutritionally adequate for gestation and lactation.

Assessment

Assessment of the suitability of the feeding plan for the queen or bitch should be conducted routinely throughout gestation and lactation. This is done primarily by observation and determination of the health and body condition score of the dam. The nutritional adequacy of the mother's diet will also be reflected in the health and vitality of the kittens or puppies. Poor or inadequate milk production during lactation may be reflected in high neonatal mortality rates, poor growth rates, and continuous vocalization indicating hunger in the offspring. If the body condition of the dam drops below 4 to 5 out of 9, consideration should be given to adjusting the amount or type of food offered (preferably more energy dense and/or more palatable) after other causes of weight loss have been eliminated.

Growth

Orphan Kittens and Puppies

Ideally kittens and puppies will be raised uneventfully by their mother and weaned to an appropriate growth diet. Occasionally they are orphaned and other feeding approaches are required. If a nursing queen or bitch is available, it is ideal to try to foster the orphaned offspring to that dam. In the event that is not possible, then they will need to be hand-raised with either tube feeding in very young or debilitated neonates, or bottle feeding in older and healthier ones. Bottle feeding is safest and easiest but can be time consuming, especially if one is managing a large litter. Tube feeding can be mastered by most clients with a little training and is a faster, albeit riskier, method to deliver nutrition.

It is recommended that a commercial milk replacer be used, as many home-prepared formulas are not adequate to meet the needs of a growing kitten or puppy. If using a home-prepared formulation, it should be reviewed and balanced if necessary by a board-certified veterinary nutritionist to ensure adequacy for growth. Cow's and goat's milk do not contain as much fat, protein, or calories as milk from queens and bitches and therefore should be avoided (Wills and Morris 1996).

Most commercial formulas contain approximately 1 kcal/ml, although there is some variation, and dilution with water will reduce the caloric density. Recommendations for feeding are variable but range from 13 to 18 ml/100 g body weight (using a formula with a caloric density of approximately 1 kcal/ml) to begin with and then gradually increasing as the orphan gains weight (Gross et al. 2010; Hoskins 2010). Every feeding should be followed with anogenital stimulation by using a cotton swab or warm cloth to encourage urination and defecation.

Assessment

The feeding program should be reevaluated frequently by assessing the health, appearance, and weight gain of the orphans. Weight gain should approximate that of nursing kittens and puppies. Nursing kittens gain approximately

18–20 g/day (Wills and Morris 1996). Nursing puppies gain approximately 1 g of body weight per 2–5 g of milk intake during the first 5 weeks following birth or 2–4 g/day/kg of anticipated adult weight for the first 5 months of their lives (Lewis et al. 1987b; Debraekeleer et al. 2010). Kittens and puppies should be active and responsive to their environment. Chronic vocalization or whimpering may be a sign of discomfort or alternatively hunger and should be an indication to reevaluate the feeding program.

Weaning to Adult

All kittens and puppies should be encouraged to start eating the food fed to the dam when they are 3 to 4 weeks of age, regardless of whether they were nursed by the dam or hand reared. This diet should be mixed with enough water to form a thick gruel. At weaning, every growing animal should be fed a complete and balanced diet designed, and preferably tested, for growth or all life stages.

Kittens

Kittens normally weigh between 90 and 110 g at birth and should gain 50–100 g until they are 5 or 6 months of age (Wills and Morris 1996). In kittens, excessive growth rates do not invoke the same consequences as in dogs; however, obesity can become a problem. Often kittens are fed free choice so monitoring is essential to catch and eliminate any excessive weight gain. Kittens should be fed a diet that meets the nutrient and energy requirements for growth or all life stages.

Puppies

Puppies should gain between 2 and 4 g/day/kg of anticipated adult weight for the first 5 months of life (Lewis et al. 1987b). If the dog should weigh 20 kg as an adult, the puppy should gain between 40 and 80 g/day. Excessive feeding during growth can lead to obesity and in larger breed dogs can result in skeletal problems (Hedhammar et al. 1974; Lavelle 1989; Kealy et al. 1992). Studies have demonstrated that controlled meal feeding of pups leads to a slower growth rate and fewer skeletal problems but does not decrease the final mature body size compared to pups fed free choice (Hedhammer et al. 1974). Please refer to Chapter 10 for a more extensive discussion of this topic.

"How much should I feed my puppy?" is one of the more challenging questions for the practitioner to answer. In order to address this question, one should start by getting a complete diet history on the dog, including the name and amount of diet it is currently being fed. The nutritional adequacy statement should be checked to ensure that it is appropriate for growth or all life stages and the number of calories consumed daily should be calculated. Assuming the puppy is at an ideal body condition, the current amount fed is likely appropriate, and the owners should be instructed to continue their feeding regime, increasing food intake gradually as the puppy grows. Alternatively, one can calculate the number of calories the dog should be eating using an equation for growth (see Chapter 3). However, this method may significantly under- or overestimate the actual energy requirement (NRC 2006). An easier approach to get an estimate is to start with the feeding directions from the food the client is feeding. Because feeding directions are designed to provide enough calories for all the dogs receiving a particular diet, there is a tendency for them to, at times, overestimate calorie needs. Regardless of which approach is chosen, both are only an approximation of the dog's actual caloric needs and will require frequent monitoring and adjustment as the puppy grows to maintain an ideal body condition.

Portion-controlled feeding is recommended for puppies in order to prevent obesity and the skeletal developmental disorders that are linked to overnutrition, especially in large to giant breed dogs. Puppies should be fed at least twice daily, and some may require three or more meals. Some individuals suggest using a time-limited feeding approach to assist with housebreaking, but one study reported that some dogs may consume more with this approach than if they were fed free choice (Toll et al. 1993). In addition, these dogs gained more weight and body fat compared to dogs receiving the same diet *ad libitum* (Toll et al. 1993).

Neutering and the Prevention of Weight Gain in Kittens and Puppies

Multiple studies have shown that intact adult pets generally weigh less than neutered animals of the same breed and size (Root 1995; Duch et al. 1978; Houpt, Coren et al. 1979; Flynn et al. 1996; Fettman et al. 1997). This is probably a combination of physiological and environmental factors. Owners are generally encouraged to neuter their pets between 6 months and 1 year of age. This time period corresponds to a natural decrease in the animal's growth rate and energy needs. If owners are not aware of this change, and continue to feed their pet the same amount of food, excess weight gain will result. Increasing age and a change in sexual status are also associated with a decrease in voluntary physical activity. Recent studies have demonstrated that ovariohysterectomy and castration in cats leads to an increase in food intake and weight gain (Fettman et al. 1997; Martin et al. 2001; Kanchuk et al. 2003; Nguyen et al. 2004).

Recently, early-age neutering (at 8 to 16 weeks of age) has become more common. One concern has been the potential of early-age neutering to influence a pet's tendency to become obese. However, a study evaluating metabolic rates, and obesity development in cats neutered at 7 weeks of age, 7 months of age, or left intact, found no difference between cats neutered between 7 weeks or 7 months of age (Root 1995). These results indicate that early-age neutering presents the same level of risk of weight gain as does neutering at the traditional age of 6 to 9 months (Root 1995).

Given the strong link between weight gain and neutering it would make sense that this milestone is a good time to discuss the risk of obesity and the opportunity for prevention in the client's pet. There are several steps that an owner can take to prevent weight gain in their pet following neutering. Changing from an *ad libitum* feeding approach to one in which the food is offered in carefully controlled meals may prevent weight gain. Alternatively, one can consider feeding a diet with a lower energy density. A recent study demonstrated a reduction in weight gain in neutered cats that were fed a low-fat, low energy density diet compared to neutered cats fed a higher-fat and more energy-dense diet (Nguyen et al. 2004).

Assessment

It is important to monitor kittens and puppies frequently during the growth process. This monitoring is facilitated by the fact that they are visiting the veterinary office frequently during this life stage for check-ups and vaccinations. Puppies and kittens should be weighed and body condition scored at every visit and the diet history form updated. Owners should also be asked about appetite and food intake (i.e., amount and enthusiasm for eating) to ensure that they are meeting their energy and nutrient needs without significant difficulty. In addition to the routine examination, one should evaluate the animal to ensure that its coat quality is good and that the puppy or kitten is bright, curious, and active. If there is excessive weight gain or a body condition score greater than 5 out of 9, owners should be directed to feed 10% fewer calories (or more if indicated based on the animal's weight, body condition, and calorie intake). Alternatively, if the animal is not growing normally or is underweight and metabolic causes have been eliminated, consideration should be given to increasing the amount of food fed by 10%. Regardless of the problem, the animal should come back for a weight and body condition score check within 2 to 3 weeks to ensure that it is returning to an ideal body condition and growing normally.

Adult Cats and Dogs

In addition to feeding a diet that is nutritionally formulated to meet the nutrient needs of dogs and cats, probably the most important feeding recommendation for this life stage is to keep animals in a lean body condition. The maintenance of a lean body condition has been proven to increase both the quantity and quality of life in dogs (Kealy et al. 2002). Currently there are no similar data in cats. Obesity has been linked to diabetes mellitus, lameness, and skin disease (Scarlett and Donoghue 1998), and it is a risk factor for hepatic lipidosis in anorexic cats (Biourge et al. 1994). One might surmise that by avoiding conditions that contribute to early mortality by maintenance of a lean body condition, one will secondarily contribute to life extension in cats as well.

There exists some controversy regarding whether it is better to feed cats dry compared to moist diets. Proponents of canned food cite the documented increase in water consumption in cats consuming such products (Kane et al. 1981), the possible prevention of urinary tract problems, and the potential voluntary reduction in food intake and consequent reduction in calories, all helping to prevent weight gain in cats. Proponents of dry food cite the dental health benefits and the ability to feed *ad libitum*, thereby more appropriately mimicking the natural pattern of food intake in the cat (Kane et al. 1981), and the esoteric pleasure of consuming food that is crunchy and requires chewing. Consideration should be given to these variables and the animal's preferences when recommending one type of food over another. However, the authors recommend exposing young cats to the different food formats to prevent texture preferences that might otherwise limit future diet options.

Assessment

Adult cats and dogs should be seen routinely for a medical evaluation. Success of the feeding program can be evaluated based on the animal's maintenance of a lean body condition and an active lifestyle. A diet history should be updated at every visit to maintain historical records on the types and amount of calories fed, in case conditions requiring dietary modification occur in the future. Frequent alterations in the diet or a significant increase or decrease in food intake may be an early indicator to the practitioner of an underlying problem.

Senior Dogs and Cats

Although the concept of aging is difficult to define, most experts agree that aging is not a disease. Aging has been defined as "a complex biologic process resulting in progressive reduction of an individual's ability to maintain

homeostasis under physiologic and external environmental stresses, thereby decreasing the individual's viability and increasing its vulnerability to disease, and eventually causing death" (Goldston 1989). It is difficult to define old age in dogs and cats. As with humans, the aging process varies tremendously from individual to individual. The aging process is influenced by an animal's breed, size, genetics, nutrition, environment, and other factors. As a general rule, larger breeds have a shorter life expectancy than smaller breeds, and mixed-breed dogs live longer than purebreds of a similar size. A survey of veterinarians revealed that clinicians believe the term "geriatric" is appropriate when applied to small dogs (<20 pounds) at 11.5 years, medium dogs (21–50 pounds) at 10 years, large breeds (51–90 pounds) at 9 years, and giant breed dogs (>90 pounds) at 7.5 years (Goldston 1989; Allen and Roudebush 1990). Other authors suggest that a dog or cat is aged when it completes 75–80% of its expected life span, or reaches 5–7 years of age (Maher and Rush 1990; Moser 1991; Laflamme 1997). While the definition of when a dog or cat becomes "mature" has not been agreed upon, there are data to suggest that our dog and cat population is getting older. Over a 10-year period, the number of pet cats over 10 years of age has increased by 15%, and the percentage of cats over the age of 15 years has increased from 5% to 14% of the population (Stratton-Phelps 1999). It has also been reported that more than 35% of dogs in the United States are older than 7 years (Lund et al. 1999). One might speculate that with earlier and more advanced care those numbers have likely increased since those surveys were published.

BOX 7.1.

The following principles should be kept in mind when considering the interaction of aging and nutrition (Moser 1991):

- Chronological age is not a reliable indicator of functional age. Changes in body composition, organ function, physical performance, and mental alertness are age related, but there is great individual variability. Within a particular individual, various organs may age at different rates.
- Nutrient requirements for older dogs and cats have not been adequately determined but most likely vary from individual to individual because of genetic, health, and environmental influences.
- Elderly dogs and cats are more variable than any other age group (e.g., puppies or kittens).
- The incidence of chronic disease increases with age.
- A properly administered geriatric nutrition program is one in which dietary recommendations are made on an individual basis, with modifications secondary to reevaluation at regular intervals.

Physiological Changes Associated with Aging

Rather than relying on chronological age to categorize a patient, older animals should be assessed as individuals using functional and physiological changes that commonly occur as the pet gets older.

Energy Requirement

In many dogs, resting and maintenance energy requirements decrease as they age (Kienzle and Rainbird 1991; Speakman et al. 2003). Multiple studies examining a variety of breeds estimated an 18–24% reduction in maintenance energy requirements compared to those of younger dogs (Finke 1991; Kienzle and Rainbird 1991; Taylor et al. 1995; Harper 1997). The change in energy requirements is also related to changes in body composition. It has been reported that there is a highly significant, negative linear correlation between age and the lean to fat ratios in dogs (Meyer and Stadtfeld 1980; Harper 1998b).

One interesting exception to a general decline in energy needs with aging was reported in a study looking at working versus pet Border Collies in the United Kingdom (Harper 1998a). Border Collies that were maintained as pets had a similar decline in energy requirements as reported in previous studies. However, working Border Collies experienced no change in energy needs with aging, supporting the author's hypothesis that dogs that remain active do not display a change in their maintenance energy requirements over time.

The degree of decline in energy requirements appears to be breed and size related based on models of energy expenditure over the lifetime of the dog (Speakman et al. 2003). It has been hypothesized that the decline in metabolic rates with age is a consequence of the declining force of selection with aging and that older animals have lower metabolic rates because they invest less in defense and repair mechanisms (Speakman et al. 2003).

The situation appears to be somewhat different in cats. Previous evidence suggested that maintenance energy requirements remained constant throughout adult life (Anantharaman-Barr et al. 1991; Taylor et al. 1995; Harper 1998a). These findings were supported by additional work that did not document a change in the lean to fat ratio in

cats with age (Munday and Earle 1991; Harper 1998b). However, more recent studies suggest that maintenance energy requirements decrease in mature cats compared to younger cats but increase again when the cats became older at approximately 10–12 years of age (Cupp et al. 2004; Perez-Camargo 2004; Laflamme 2005). This increase was not linear, but rose dramatically between the ages of 12 and 15 (Perez-Camargo 2010). These same researchers also reported that cats that lose body fat, lean mass, and bone mass are at a greater risk for earlier mortality (Perez-Camargo 2010).

Digestion and Absorption

Changes in the alimentary system may contribute to inadequate food intake, decreased appetite, and systemic disease. As animals age, there is an increased incidence of dental calculus, periodontal disease, periodontitis, and tooth loss. These alterations, combined with a reduction in the amount of functional saliva, will often contribute to a decline in food intake.

Age-related changes in digestive physiology, hormones, and gut microbiota may directly or indirectly reduce digestive capacity (Fahey et al. 2008). Unlike in humans, structural changes in the canine digestive tract are not very pronounced during aging, and atrophy and fibrosis are rarely seen (Mundt 1991). Nevertheless, on histological examination, changes are evident in the salivary glands, small intestine, liver, and pancreas of older dogs (Mundt 1991). Despite these changes, advancing age does not reduce apparent nutrient digestibility in dogs (Lloyd and McCay 1954, 1955; Sheffy et al. 1985; Buffington et al. 1989; Taylor et al. 1995). In fact, several studies reported higher apparent digestibility coefficients for protein and fat (Lloyd and McCay 1954; Sheffy et al. 1985) and energy (Sheffy et al. 1985) although explanations for why this occurred are not provided.

Morphological changes, transit times, and the secretory capacity in the feline gastrointestinal tract have not been as well studied. Several studies have demonstrated no significant difference in orocecal transit times in young compared to older cats (Papasouliotis et al. 1996; Peachey et al. 2000). Nonetheless, several studies have reported reductions in the digestibility of protein, fat and starch in older cats (Taylor et al. 1995; Peachey et al. 1999; Patil and Cupp 2010; Teshima et al. 2010). One study reported a positive correlation between fat digestibility and serum vitamin E concentrations (Patil and Cupp 2010). This same study also reported a positive correlation between fat and protein digestibility and plasma vitamin B12 concentrations (Patil and Cupp 2010).

Integument and Musculoskeletal System

Multiple changes are visible in the integument and musculoskeletal system of older dogs and cats. The skin loses elasticity and becomes less pliable (Markham and Hodgkins 1989). Loss of elasticity is often accompanied by hyperkeratosis of the skin and follicles. Follicles often atrophy, resulting in hair loss. Loss of pigment results in the production of white hairs, often seen around the muzzle of older dogs and cats. Along with a decline in lean body mass, there is a reduction in bone mass. The cortices of the long bones become thinner and more brittle (Case et al. 1995). This may be due to the reduced absorption of calcium from the intestine of some older pets (Case et al. 1995). Arthritis is a common occurrence in older animals and may affect the pet's desire (or ability) to eat. Obesity can compound the effects of arthritis, or, conversely, arthritic pets may experience a reduction in appetite leading to severe weight loss.

Renal System

Renal failure is a major cause of illness and mortality in geriatric cats, and of one of the three leading causes of death in older dogs (Morris Animal Foundation 1998). Despite this statistic, little is known about renal function in the general population of geriatric companion animals (Brown 1997). It is important to remember that gradual renal senescence with normal aging is opposed by the tremendous reserve capacity of the kidneys. Studies have shown that dogs and cats have 10–20 times more renal tissue than is required to sustain normal life (Brown, Finco et al. 1991). Studies have suggested that normal kidney aging may lead to nephron loss of up to 75% before clinical or biochemical signs occur in older animals (Cowgill and Spangler 1981). Therefore, practice approaches that assume inadequate renal function in geriatric patients may have adverse effects.

Immune Response

Alterations in the immune system associated with aging are well recognized (Cowan et al. 1998). These changes may contribute to the increased incidence of infectious diseases and tumors (Meydani and Hayek 1997). Older dogs and cats have reduced blood $CD4^+$ T cells, elevations in the $CD8^+$ subset, and reductions in the CD4:CD8 ratio (Day 2010). The cutaneous delayed-type hypersensitivity response is reduced, while humoral immune responses are not significantly impacted by age (Day 2010). Serum and salivary immunoglobulin (Ig)A production increases, and IgG concentration remains unaltered (Day 2010). Little is known about "inflammaging," which is defined as the

effect of cumulative antigenic exposure and onset of late life inflammatory disease in dogs and cats (Day 2010).

Sensory

The aging process results in a general reduction in the sensations of vision, hearing, taste, and smell. These changes occur in humans and companion animals alike (Markham and Hodgkins 1989; Harper 1996). Involution of nervous tissue is believed to be responsible for the diminution of taste and smell responses (Markham and Hodgkins 1989). These may contribute to a reduction in the desire to eat and result in weight loss in older animals. Geriatric animals often experience a decreased sensitivity to thirst, which has the potential to contribute to a state of dehydration. Patil and Cupp (2010) reported no difference in fecal water losses between adult cats (1–7 years) and geriatric cats (>12 years). However, urine volumes were significantly higher in the older cats. They hypothesized that this may be the result of a decreased ability for the aged kidneys to concentrate urine even in the absence of renal insufficiency. Aging also diminishes an animal's thermoregulatory capacity and subsequent tolerance to heat or cold (Markham and Hodgkins 1989).

Behavior

Behavioral changes are common in older pets and are a frequently overlooked physiological alteration that may affect the animal's ability, or desire to obtain adequate nutrition. Behavioral changes can be the result of many disorders including systemic illness, organic brain disease, true behavioral problems, or cognitive dysfunction syndrome (CDS) (Neilson et al. 2001; Gunn-Moore et al. 2007). Cognitive dysfunction syndrome is a term applied to age-related deterioration of cognitive abilities, characterized by behavioral changes, where no medical cause can be determined (Gunn-Moore et al. 2007). Animals that are suffering from chronic pain may become irritable and reluctant to eat properly, if at all. Changes in the home environment, such as the loss of another pet or owner, or the introduction of a new animal or person, can induce an alteration in eating behavior or a state of anorexia (Houpt and Beaver 1981).

Nutrient Requirements of Older Pets

Elderly pets have the same nutrient needs as their younger counterparts (NRC 2006). However, the quantities per unit of body weight may change, and the way they are provided may require modification. Feeding recommendations for this life stage are not unlike any other life stage in that each animal should be treated as an individual and as a consequence will vary from patient to patient.

Energy

If an animal's energy needs decrease without a reduction in caloric intake, obesity will develop. Some diets for mature dogs and cats are designed with higher fiber levels to combat this problem by decreasing the food's energy density. However, not all animals will gain weight as they age; many remain weight stable and a large number will experience varying degrees of weight loss. This population of pets may benefit from more energy-dense, palatable diets to help them maintain or gain weight. Similar to other life stages, dogs and cats should be fed to maintain a lean body condition through their senior years.

Protein

The decline in lean body mass that occurs with aging results in a loss of protein "reserves" in the body frequently required to combat stress and disease. Results from one study suggest that older dogs have higher protein requirements than adult dogs (Wannemacher and McCoy 1966). The investigators of this study found that older dogs required up to 50% more protein than young dogs to maintain labile protein. A more recent study examined 8-year-old Pointers fed either 16.5% or 45% protein calories over a 2-year period (Kealy 1999). Both groups had a reduction in lean body mass. Even the group consuming a higher percentage of their calories from protein lost 3.5% of their lean body mass. While neither of these studies provide definitive recommendations for protein requirements in older dogs, they do suggest that the amount of protein in the diet is important and may impact health and body condition.

Similarly, recommendations regarding protein requirements for older cats are lacking. One study reported maintenance of lean body mass in adult cats consuming 36% protein on a dry matter (DM) basis (Hannah and Laflamme 1996). Cats consuming lower amounts of protein (22% and 28% DM) maintained nitrogen balance but lost lean body mass (Hannah and Laflamme 1996). This study suggests that the amount of protein consumed may impact lean body mass. A second study looking at the impact of dietary protein concentrations on the preservation of lean body mass following neutering also reported a loss of lean body mass on average of 1.2% when cats were fed a diet containing 30% protein DM (Nguyen et al. 2004). When the cats were fed 53% protein DM they reported an average accumulation of 4.2% of lean body mass.

The quality of protein is an important consideration. To reduce bacterial metabolites, the protein should have a high biological value and a high prececal digestibility. Most commercial pet foods are formulated to exceed minimum requirements, so adequate protein is usually not

a concern. However, if energy intake is reduced secondary to a decreased metabolic rate or food intake, the protein-to-calorie ratio may need to be adjusted to meet the protein requirement. Furthermore, some high-energy foods with reduced protein concentrations, such as products designed to address renal or liver failure, do not provide as high a level of protein, especially if food intake is reduced.

There is a great deal of controversy concerning the restriction of protein in elderly animals as a measure to prevent renal disease. Although there is evidence that protein restriction is effective in minimizing the clinical signs of renal failure once disease is present (Elliott et al. 2000; Jacob et al. 2002), there is no evidence that protein restriction is of any benefit to healthy older dogs and cats. Considering that older dogs may have an increased protein requirement, that there is loss of lean body mass in both dogs and cats with advancing age, and that a decline in protein digestibility exists in older cats, the authors do not recommend protein restriction in older dogs and cats unless indicated by an underlying disease. In some cases, other dietary changes, such as phosphorus restriction with renal disease, may be a more important strategy.

Fat

Dietary fat is necessary in every animal's diet to provide essential fatty acids, energy, a vehicle for fat-soluble vitamin absorption, and to enhance palatability. Fat increases the energy density of food. In animals prone to obesity this can pose a problem. A slight reduction in dietary fat may be necessary to aid in the prevention of weight gain. On the other hand, in underweight animals a diet with a high energy density may be beneficial.

Supplementation With Antioxidants and Fatty Acids

Recently, there has been an advent of diets on the market enhanced with antioxidants to support immune function. The implication is that such enhancement will extend (or reverse) the aging process and prevent or reduce the likelihood of disease. A number of these studies were conducted in young animals, but a few have looked at the effects on older dogs and cats. Dietary supplementation of vitamin E at 250 IU/kg in the diet stimulated lymphocyte genesis in young and old cats (Hayek et al. 2000). β-carotene supplementation restored immune response in older dogs when compared to their age-matched controls and younger counterparts (Massimino et al. 2003). Another study examined the effect of n-3 and n-6 fatty acids on immune parameters in young and old dogs. Supplementation with n-3 fatty acids (n-6:n-3 ratio of 5:1) did not affect IL-1, IL-6, or TNF-α production but did reduce malondialdehyde concentrations in older dogs, an indicator of antioxidant status (Kearns et al. 2000).

A second area of product development has focused on addressing canine cognitive dysfunction disorder. Recent research has provided some support for the use of docosahexaenoic acid (DHA) in the improvement of memory and health status (Araujo et al. 2005) and medium-chain triglycerides in improving performance in cognitive testing in dogs (Pan et al. 2010). Medium-chain triglycerides may help with this condition by providing the brain with ketones as an alternate energy source (Pan et al. 2010). It is unclear if these fats may also aid in the prevention of cognitive dysfunction disorder; further research is needed.

Another approach to treating canine cognitive dysfunction has been the development of diets that incorporate antioxidants and mitochondrial cofactors. One diet has been shown to improve canine cognitive dysfunction both in laboratory and clinical trials (Head 2007). The goals of the diet are to use antioxidants and mitochondrial cofactors to reduce the production of reactive oxygen species (ROS) and facilitate their clearance from the body to slow the progression of age-related pathologies and cognitive decline by reducing oxidative damage (Christie et al. 2010).

Despite documented alterations in immune and antioxidant parameters in dogs and cats, as well as clinical improvement in cognitive function in dogs, existing studies do not address the possible preventive or long-term effects of these supplements and diets, and if animals consuming them will live longer or have a lower incidence of disease. Long-term studies are necessary to address some of these questions. However, the lack of data in some cases is not a fatal flaw but does necessitate careful evaluation of the food and its claims and supportive research. In many cases the diets or supplements are unlikely to be harmful but may not help in all animals.

Feeding Recommendations for Mature Dogs and Cats

The major objectives of a feeding program designed for an older pet should include the maintenance of health and an optimal body weight, the slowing or prevention of chronic disease, and the improvement of clinical signs of diseases that may already be present. When determining dietary recommendations for older pets, it is important to complete a thorough nutritional evaluation of the animal. A thorough evaluation includes evaluation of the pet, diet, and feeding management program. Evaluation of the animal includes a complete medical history and thorough physical examination (including body weight and body condition score).

Elderly dogs or cats that are healthy, in a lean body condition, and eating an appropriate diet do not need to be

changed to another diet simply based of their age. It is not appropriate in many cases (especially in dogs) to feed older animals *ad libitum*, as this predisposes them to obesity. Owners should be instructed to monitor their animal's food intake, as alterations may indicate the presence of an underlying disease process. Proper care of the pet's teeth and gums is essential to prevent a reduction in food intake secondary to dental problems. Based on the animal's physical condition, regular and sustained periods of exercise should be recommended for all patients. Regular exercise helps maintain muscle tone, optimal body weight, and enhances circulation. If a dietary change is necessary, it can be done gradually over a period of at least a week.

Once it has been determined how much to feed, feeding management should also be discussed with the owner. Dividing the amount of calories into small multiple meals throughout the day will help minimize hunger and begging, as well as possibly increase the metabolic rate. Treats and snacks are important to the human–animal bond and should not be eliminated. It is important, however, that the calories contributed by treats be accounted for. As with all life stages, treats and snacks should never make up more than 10% of the animal's daily calorie intake.

Weight Loss

In contrast to obese animals, geriatric dogs and cats may have the problem of unintended weight loss, and this may often be overlooked. This weight loss may be associated with an increase or decrease in food intake. If the animal is consuming more food secondary to a recent change to a food with a lower caloric density, this response could be normal. Less energy-dense pet foods may be inappropriate for an animal with unusually high energy needs or an active lifestyle. Alternatively, an underlying metabolic process may be present.

A decline in food intake may occur for many reasons. In human geriatric medicine they use the mnemonic of nine "D's" to describe the common causes of weight loss in their patients: dentition, dysgeusia (distortion of taste), diarrhea, disease, depression, dementia, dysfunction, drugs, and "don't know" (*Nutrition and the MD* 1994). Most of these nine "D's" can be applied to our veterinary patients as well. If a specific cause for unintended weight loss cannot be determined, symptomatic treatment for weight loss should be instituted. Feeding an energy-dense, nutrient-dense, highly palatable food more frequently would be appropriate. Examples include, but are not limited to, diets designed for growth, critical care formulas, or offering cat food to dogs.

Feeding and environmental modifications may be helpful as well. Food intake can be stimulated by serving fresh food, moistening dry food, warming food to body temperature, and having the client encourage the pet during eating. Feeding the animal away from the other household pets in a noise- and stress-free environment may also be helpful. One should make sure that the pet's nasal passages are clear, as dogs and cats rely on olfaction to select food. Bowls for cats should be wide and shallow so they do not touch their whiskers, as that can decrease food intake.

Assessment

Recently experts have been recommending that an appointment for an elderly pet include blood, fecal, and urine analyses on a routine basis (Fortney 2010). Although many of these tests are not sensitive indicators of nutritional status, they may indicate the presence of a subclinical process that may be nutrient responsive. Similar to other life stages, senior dogs and cats should maintain a lean body condition. Action should be taken promptly in cases where animals are gaining weight by implementing calorie restriction. Alternatively, previously healthy animals that begin to experience unintended weight loss or loss of lean body mass should receive a thorough examination and diagnostic work up. Nutritional strategies to address any underlying conditions or that encourage an increase in food intake should be instituted immediately.

SUMMARY

- A complete diet history should be obtained and updated at every visit in every patient.
- The best diet will vary from animal to animal. Each dog and cat should be evaluated as an individual.
- Careful consideration should be given to the animal, the diet, and the animal's environment when making a dietary recommendation.
- Dietary recommendations should be appropriate for the animal's life stage.
- Treats and snacks are an important part of the human–animal bond and should be included in a feeding program. The amount of energy provided from snacks and treats should never exceed more than 10% of the patient's daily calorie intake.
- Regardless of life stage, all dogs and cats should be fed to maintain a lean body condition.
- Each patient's feeding program should be assessed at every visit and adjustments made as indicated based on the animal's body condition, life stage, and general health.

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Commercial and Home-Prepared Diets

8

Andrea J. Fascetti and Sean J. Delaney

INTRODUCTION

According to a recent industry organization survey, 71.4 million (62%) of American households have a pet (American Pet Products Association 2010). That equates to 77.5 million dogs and 93.6 million cats. Advice regarding what and how much to feed is one recommendation every dog and cat owner should receive from their veterinarian. The discussion regarding what to feed an individual pet can be somewhat overwhelming as there are so many pet foods on the market. Many clients wish their veterinarian would recommend a specific diet (Crane et al. 2010), and in a recent study veterinarians were the most frequently cited source for information about pet food (Laflamme et al. 2008). While it helps to have specific recommendations on hand for clients after reviewing their pet's diet history, many clients may still want to discuss foods or feeding approaches that are unfamiliar to the veterinary practitioner. There are approximately 175 pet food manufacturers in the United States (Crane et al. 2010), so it is impossible for the practitioner to be familiar with every company and its products. Regardless, one should have a working understanding of the variety of feeding practices and food types available to one's client to facilitate conversations. This chapter will review the various types and market segments of commercial pet foods, home-prepared diets, and special considerations with respect to feeding raw food.

COMMERCIAL DIETS

According to a recent study, 93.2% and 98.8% of dogs and cats in the United States and Australia consume more than half of their daily calories from commercial pet foods (Laflamme et al. 2008). Commercial pet foods are available in four basic forms: dry, moist, semi-moist, and raw. Understanding the general characteristics, and the potential advantages and disadvantages of each food type is helpful for client communication and diet recommendations.

Types of Pet Foods

Dry Food

Dry foods were the most common type of pet food fed to dogs in a recent owner survey (Laflamme et al. 2008). Dry pet foods on average contain between 3% and 11% moisture and more than 89% dry matter. This is the food type of choice for free feeding. In general, dry pet foods are the most economical form of food to feed due to lower packaging, raw material storage, and freight costs. Some, but not all, dry pet foods may offer dental hygiene advantages. Dry foods may be less palatable to some dogs and cats. This characteristic can be an advantage in pets that are overweight or obese but a disadvantage in finicky eaters. In some (but not all) cases, manufacturers may use harsh and improper cooking and drying techniques that can result in a loss of nutrients (poor quality foods may have a low digestibility and therefore a reduction in nutrient availability).

Moist Foods

Historically, moist diets were often referred to as "canned" products, and their moisture content range anywhere from 60% to 87% (Crane et al. 2010). The term "canned" may no longer be appropriate given the wide variety of

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products that now contain a similar water content, such as pet food in trays and tubes (the latter frequently referred to as "chubs"), so the term "moist" will be used instead. Cats are significantly more likely to receive half of their diet from moist food compared to dogs (Laflamme et al. 2008).

Moist diets generally have a high level of palatability and contain high concentrations of meat and/or meat by-products. Compared to dry or semi-moist products they are often higher in fat, sodium, and phosphorus (Crane et al. 2010). These diets usually have a very long shelf life as they are produced using heat sterilization and vacuum preservation. Moist products often have a lower energy density than dry or semi-moist foods on an as-fed basis. The higher water content and lower energy density may be useful in providing satiety and reducing calorie intake, which may be helpful in preventing obesity. Moist foods also are recommended as a method to deliver more water to a patient with urinary tract health concerns. A lower energy density, combined with the costs of production, create a situation where moist products often have a higher price per calorie compared to dry and semi-moist diets (Crane et al. 2010). This can be a major disadvantage for some owners if they are feeding moist food exclusively. The perceived advantage of being less energy dense can actually become a disadvantage if the animal is a finicky eater or underweight. Many owners do not like the odor and messiness of moist products and unused food must be stored in the refrigerator. Another potential concern can be seen in pets being exclusively fed some of the gourmet moist foods or chubs. While often very palatable, in some cases these foods are not nutritionally balanced or complete. Furthermore, such feeding practices can also encourage some cats and dogs to develop fixed food preferences so they will not eat another diet.

Semi-Moist Foods

Most semi-moist foods contain 15–35% water. These products are softer in texture than dry pet foods, contributing to their acceptability and palatability. The inclusion of organic acids and humectants such as simple sugars, glycerol, or corn syrup bind water molecules in the food and make them unavailable for use by microorganisms. This processing technique helps to control water activity (the amount of water available to microorganisms) and reduces the growth of molds (Crane et al. 2010). Over the years there has been a reduction in semi-moist products on the market, but it is still not uncommon to find them as inclusion pieces in dry foods or as treats. Semi-moist foods generally have a high level of palatability, and owners find them convenient because they are often packaged in single serving portions. Some owners also favor semi-moist foods because they lack the odor and mess associated with moist products and come in shapes similar to foods they consume (burgers, vegetables, etc.). Semi-moist foods can be expensive and will become dry if allowed to sit out for several hours. The high palatability of these foods can be an advantage in picky eaters or underweight animals. This advantage becomes a disadvantage in obese-prone pets. These products should not be used in diabetics if they use a large amount of sugar or syrup.

Raw

These diets are often referred to by the acronym "BARF," which stands for "bones and raw food" or "biologically appropriate raw food" diet. It is unclear how many people are feeding their pets raw food diets; however, based on the growing number of commercially available raw food diets, one can surmise it is growing, but likely is still fed to only a small percentage of pets.

There are two forms of commercial raw foods on the market. The first are commercially available, "complete" foods, intended to be the sole source of nutrition, like any other commercial diet. These products are supplied in several forms. The most common include fresh raw food; frozen raw food, which the owner thaws before serving; or freeze-dried raw food that can be rehydrated with water upon serving if the owner so desires. Combination diets are the second type of commercial raw food diet commonly used. With this approach the client purchases a supplement mix that is then combined with raw meat that they purchase themselves to yield a nutritionally complete diet. The supplement may or may not contain carbohydrates. This approach is designed to allow the owner to rotate protein sources or choose protein sources with particular characteristics (e.g., organic, locally grown, etc.). Proponents of raw food diets proclaim many health benefits associated with this feeding regime, stating that dogs and cats are carnivores and as such they evolved eating raw food. However, there have been no studies to date to support that this feeding approach has any long-term health benefits compared to feeding other types of pet food. Potential disadvantages will vary with individual raw diets but may include the risk of nutritional imbalances, cracked or fractured teeth, gastrointestinal obstructions and perforations, bacterial contamination, and other potential zoonotic diseases (such as parasites). These concerns are discussed later in this chapter.

Terminology

Deciphering some of the terminology and descriptors used on pet food labels or in advertising and product-associated literature can be challenging. A full discussion of pet food labels is provided in Chapter 6, but some of the terminology associated with marketing and used to categorize pet foods is discussed here.

It is difficult for veterinarians and consumers alike to know which marketing terms and descriptors such as organic, natural, holistic, human grade, premium, and super premium are regulated terms and which are solely marketing. Currently, only the terms "natural" and "organic" have regulatory guidelines associated with their use.

The Association of American Feed Control Officials (AAFCO) defines the term "natural" as:

> A feed or ingredient derived solely from plant, animal, or mined sources, either in its unprocessed state or having been subject to physical processing, heat processing, rendering, purification, extraction, hydrolysis, enzymolysis, or fermentation, but not having been produced by or subject to a chemically synthetic process and not containing any additives or processing aids that are chemically synthetic except in amounts as might occur unavoidably in good manufacturing practices" (AAFCO 2010).

Natural pet foods are sometimes marketed with the claim that they contain no artificial ingredients. This may or may not be true depending upon the company. One of the common additives that owners are concerned about are fat preservatives such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and ethoxyquin. Products that do not contain a fat preservative will have a decreased shelf life because of problems with rancidity. The definition of "natural" includes ingredients that are subject to traditional processing methods such as rendering and extraction. Owners are often unaware that "natural preservatives" such as vitamin E or mixed tocopherols, vitamin C, or rosemary extract may also be processed and/or extracted. The term "natural" also permits a disclaimer clause for products that contain synthetic components in order to assure nutritional adequacy, such as "with added vitamins and minerals." "Trace nutrients" may also be added to this disclaimer when purified amino acids such as taurine are added. Finally, veterinarians and owners also must be cautious of products that contain natural additives such as herbs, because the safety of many of these compounds has not been tested.

According to AAFCO, the term "organic" has been defined as:

> A formula feed or a specific ingredient within a formula feed that has been produced or handled in compliance with the requirements of the USDA National Organic Program (Title 7, Part 205 of the Code of Federal Regulations) (AAFCO 2010).

Under these guidelines, a food may carry the following organic designations (United States Government Printing Office 2010):

- 100 percent organic: must have 100% organic ingredients and additives, including processing aids
- Organic: at least 95% of the content is organic by weight
- Made with organic: at least 70% of the content is organic, and the front product panel may display the phrase "Made with Organic" followed by up to three specific ingredients
- Less than 70% of the content is organic: may list only those ingredients that are organic on the ingredient panel with no mention of organic on the main panel

Only the first two categories are entitled to use the USDA seal on their packaging.

The terms "human grade" and "human quality" are used with increasing frequency these days on food labels and marketing materials. Currently there are no official definitions regulating these terms, and according to AAFCO these terms are not permitted (AAFCO 2010). Conversely, based on a recent court case, they are not legally prohibited either. The Ohio Department of Agriculture refused to allow one company to use the term "human grade" on its foods (Pet Food Industry 2007). The matter ended up in court where it was determined that the labels were not untruthful or misleading and that the company had a constitutional right to make truthful statements about the quality of its products on the labels. So these terms continue to appear on labels and marketing material. However, since there is no legal definition for the term "human grade," it is likely to be interpreted and used differently from company to company.

Other terms that have no legal definition include "premium," "super premium," "gourmet," and "holistic." These labels are used on a variety of foods with different nutrient profiles, ingredients, and quality. They can even appear on foods intended for supplemental feeding only. A client who is relying on these terms to select a diet may unknowingly choose a food that if fed solely could result in a nutritional deficiency in the long term. Further concern has been expressed about the term "holistic," as it may imply a therapeutic benefit when none may exist (Crane et al. 2010).

Market Segments

Pet foods are sold through a variety of market segments, and many owners will judge the quality of a food based on where it is purchased and how much money it costs (known as the Veblen effect). It is incorrect to assume that the amount of money spent on a diet will always equate with the quality of the food. The bottom line is that the quality among any group of diets sold in a particular outlet, whether it be a grocery store or an exclusive pet store, is going to be variable. Quality pet foods that can support all the life stages of dogs and cats can be found in all market segments or channels. A detailed discussion on how to evaluate pet foods and recommend diets to clients is covered in Chapters 1 and 7.

HOME-PREPARED DIETS

With the advent of complete and balanced commercial pet foods, the use of home-prepared diets has declined. However, over the past several years there has been a growing segment of pet owners who are electing to home prepare diets for their pets; home preparation of food can include cooked or raw food feeding. A recent telephone survey of 1,104 pet owners in the United States and Australia found that fewer than 3% of dogs and cats received at least 50% of their daily diet from home-prepared foods (Laflamme et al. 2008). On the other hand, 30.6% of dogs and 13.1% of cats received "noncommercial" foods (home-prepared foods, leftovers, and table scraps) as part of their main meal. In this study, 17.4% of dogs and 6.2% of cats received over one-quarter of their daily diet from these noncommercial foods. While this number may seem low to some, it is important to note that this survey was conducted prior to the major pet food recall of 2007. Many nutritionists feel that this number has increased since that time.

There are many reasons why owners wish to prepare meals at home for their pets. Some of the more common ones include the negative press against commercial pet foods, the belief that home-prepared foods are closer to the natural diets of ancestral dogs and cats, the feeling of a stronger bond between the owner and pet, and the ability to avoid undesired ingredients such as additives and preservatives or to use desired ingredients like raw ingredients (Laflamme et al. 2008). Many owners wish to follow philosophies that they incorporate into their personal approach to eating and apply those to their pet (e.g., vegetarian, low cholesterol, organic, etc.) or believe that home preparing a diet is cheaper than purchasing a commercial product.

Most nutritionists agree that it is in the animal's best interest to eat a commercially available food if at all possible. A very important point to remember is that home-prepared diets have not typically undergone animal feeding trials or even laboratory analysis to confirm that they support the life stage for which they were designed. However, there are a number of medically appropriate reasons to institute a home-prepared diet in some patients. The major indication for placing an animal on a home-prepared diet is a medical condition that has special nutritional concerns not addressed in a commercial or veterinary therapeutic diet. One of the more common conditions where home-prepared diets have been extremely useful is in managing adverse food reactions. By feeding a home-prepared diet one can select a protein and carbohydrate source not available in commercial foods, avoid additives and preservatives, and maintain control over the type and amounts of ingredients used. In addition, home-prepared diets are often the only option for animals with multiple medical conditions. By selecting a commercial diet to treat one condition, the practitioner may be feeding in a method that is contraindicated for another. A common example is an animal with hyperlipidemia, a history of severe recurrent pancreatitis, and renal disease. Home-prepared diets are also useful for patients with medical conditions that necessitate the use of a veterinary therapeutic prescription diet, but the diet is not well accepted by the pet for any number of reasons.

Nutritional Adequacy

Nutritional adequacy should be the first concern of every practitioner who has a patient that consumes a home-prepared diet. Only 16 of 54 pet owners who were feeding their pets a home-prepared diet in one owner survey were using a recipe designed for dogs or cats (Laflamme et al. 2008). Eight were obtained from a veterinarian, three from the Internet, and five from other sources (Laflamme et al. 2008).

The practitioner should be concerned about where clients obtain their recipes. Frequently, the recipes selected are from unknown or questionably reputable sources. In one survey, 89% and 93% of home-prepared elimination diets used for initial testing in dogs and cats, respectively, were not complete and balanced for adult maintenance (Roudebush and Cowell 1992). Nutritionally adequate home-prepared elimination diets for long-term use were only recommended 65% and 46% of the time in dogs and cats, respectively (Roudebush and Cowell 1992). A second prospective study recruited owners to home prepare their dogs food for a 30-day period. The home-prepared diets were evaluated and compared to the AAFCO's nutrient profile recommendations (Streiff et al. 2002). Thirty-five of the diets fell below AAFCO recommendations with respect to calcium, phosphorus, potassium, zinc, copper, and vitamins A and E. These nutrients were not compared

to NRC recommendations, but closer inspection of the results suggests that in some cases nutrient concentrations would have exceeded NRC minimums (NRC 2006). A more recent study specifically evaluated 49 maintenance and 36 growth diets for dogs and cats (Lauten et al. 2005). These diets were obtained from books that are frequently used by veterinarians recommending home-prepared recipes for their patients. Compared to AAFCO requirements for the respective life stage, 55% were found to be inadequate in protein or amino acids, 64% were inadequate in vitamins, and 86% were inadequate in minerals. These same diets were then compared to 1985/1986 National Research Council Nutrient Requirements of Dogs and Cats, respectively. In this case 34% were deficient in amino acids (taurine in all cases), 45% in vitamins, and 21% in minerals. Concerns with regard to nutritional adequacy apply to raw, home-prepared diets as well. One study evaluated the nutritional adequacy of five raw food diets. Two were commercial products, the remaining three home prepared. All five diets had essential nutrients that were analyzed to be below AAFCO minimum recommendations (Freeman and Michel 2001). The home-prepared diets had excessive concentrations of vitamins D and E, as well as inappropriate calcium to phosphorus ratios.

More and more reports are beginning to appear in the literature with respect to the clinical consequences of feeding home-prepared diets that are not nutritionally adequate for the animal's life stage. Growth is one period where concerns are frequently reported, as this is one of the most nutritionally demanding life stages, and deficiencies and excesses are manifested quite rapidly (Tomsa et al. 1999; McMillan et al. 2006) (see Box 8.1 for an example).

BOX 8.1.

The authors managed a case in a litter of feral kittens rescued by a local organization. One, 2 1/2-month-old, female intact kitten was presented for evaluation. The owner acquired the kitten at approximately 7–10 days of age (also fostering three other kittens of similar age). All kittens received a commercial colostrum and milk replacement formula (powder form). The kittens were weaned onto a home-prepared diet consisting of approximately 60% store-bought ground meat (beef, chicken, or turkey), and 40% fresh seasonal vegetables (carrots, green leafy vegetables, broccoli, kale, and/or celery root). Cooked bone meal (ground bones from the store) was also fed intermittently.

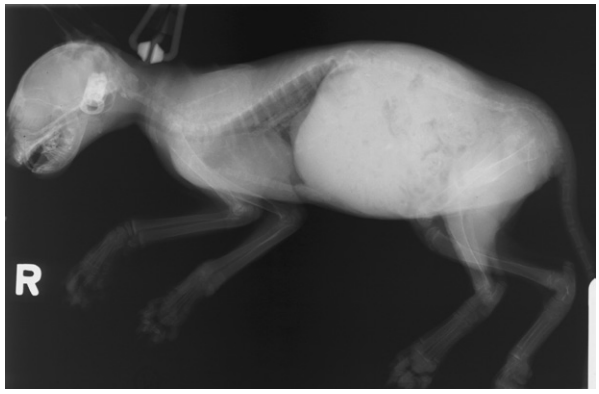
The first symptoms of lameness developed at approximately 2 1/2 months of age when the kitten could not use her hind legs. She appeared to have feeling in her legs, could move them a little without bearing weight, and had normal bowel control. The following day another kitten in the household started to display similar signs with a hind limb lameness, and approximately one week later, a third kitten began to show similar signs with a front limb lameness. The lameness varied in each cat, affecting different limbs, and varying in severity from day to day. The kittens all had good appetites and energy levels. The owner reported that they still played (although they did not move their legs) and would drag themselves to the litter box.

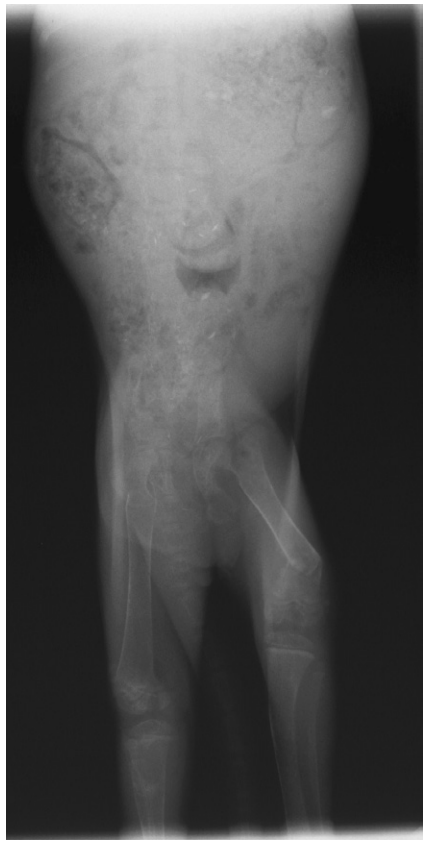
On presentation, the kitten was bright and alert, with a body condition score of 4 out of 9. Physical examination revealed pain and a probable fracture in the left femur as well as pain in the lumbosacral area. The remainder of the physical and neurological examination was normal. With the exception of a high alkaline phosphatase (expected in a kitten of this age), the blood work was all within normal limits. Radiographic evaluation reported severe generalized decreased bone opacity with thin cortices. There was a mid-diaphyseal folding fracture of the left femur, a fracture of the left ileum and possible compression of several of the sacral vertebrae, additional radiographs were recommended for further evaluation. Bone fragments were noted in the gastrointestinal tract (Figs. 8.1 and 8.2).

A computer evaluation of a sample meal from the diet history was completed and revealed deficiencies in all the essential minerals and vitamins. The authors noted that while bone chips appeared in the gastrointestinal tract on the radiographs, the availability of calcium from that bone had to be questionable given the clinical signs. Based on the history, examination findings, and diet evaluation, a diagnosis of nutritional secondary hyperparathyroidism was made.

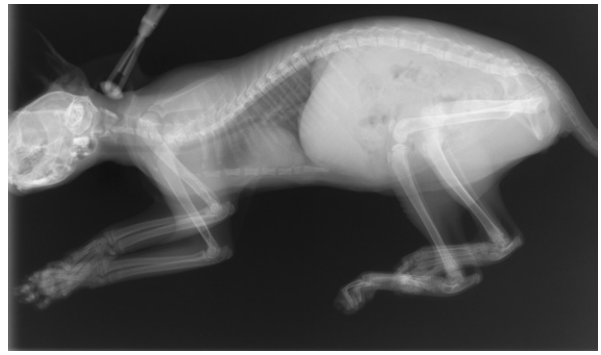
Due to financial concerns, no additional radiographs and diagnostics were performed. The caretaker was instructed to cage rest all of the kittens and to place them on a commercial kitten diet that had undergone and passed feeding trials for growth. Concerns about feeding nutritionally inadequate and raw food diets were also discussed.

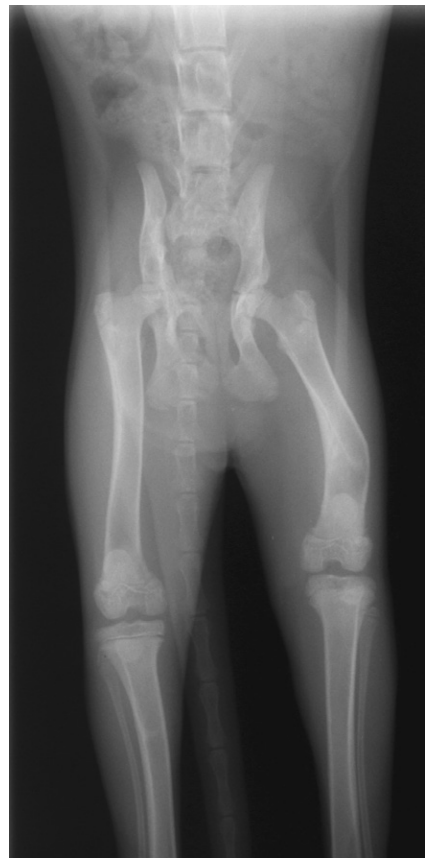
The same kitten returned approximately one month later. She had grown and her behavior had returned to normal. Repeat radiographs reported a normalized bone density and repair of the fractures (Figs. 8.3 and 8.4).





Figs. 8.1 and 8.2. Lateral and ventral-dorsal view of a 2.5-month-old kitten fed an unbalanced, raw home-prepared diet. Note the generalized decreased bone opacity and thin cortices, mid-diaphyseal folding fracture of the left femur, fracture of the left ileum, and possible compression of several of the sacral vertebrae.





Figs. 8.3 and 8.4. Lateral and ventral-dorsal view of the same kitten taken approximately one month following the consumption of a commercial, all life stage dry diet. Note the normalized bone density and healing fractures.

However, some of the published cases are in adults, thereby underscoring the risk involved for individuals at any life stage. Reports in younger animals are frequently related to inadequate calcium or improper calcium to phosphorus ratios (Tomsa et al. 1999; McMillan et al. 2006), leading to lesions or fractures in the long bones. Comparatively, clinical signs secondary to calcium deficiency in adults are frequently manifested as rubber jaw syndrome with resorption of the mandible or maxilla (de Fornel-Thibaud et al. 2007). While most reports are related to major mineral deficiencies or imbalances, other nutritional problems can occur. There is an interesting case series of growing and juvenile cats with pansteatitis associated with the consumption of high levels of unsaturated fatty acids in fish or pork brain based diets (Niza et al. 2003).

Managing Patients Using Home-prepared Diets

A diet history should be obtained on every patient, each time they are seen in one's practice. If a client mentions that they are preparing food at home for their pet, it is recommended that a copy of the detailed recipe (including the source) be obtained from the owner and entered into the patient's permanent medical record. The owner should also be asked about their reasons for opting to prepare food at home rather than purchasing a diet for their pet. This will help the practitioner understand the owner's motivations, and such knowledge may be useful in directing them to a more appropriate alternative if necessary.

As the primary care provider, the practitioner is the first line of defense with respect to identifying and stopping feeding practices that are not nutritionally adequate. Chemical analysis of the home-prepared diet is one of the best methods of evaluating the adequacy of a particular recipe. However, it is cost prohibitive for most owners. It is virtually impossible to determine if a recipe meets a patient's nutrient needs by inspection alone; however, one can often identify areas of concern based on a quick overview. This type of review can provide a foundation for the practitioner's recommendation to have the diet evaluated and revised by a veterinary nutritionist or evaluated by the veterinarian themselves using a nutritional software program.

During initial inspection of the diet, one should try to identify the protein, fat, carbohydrate, vitamin, and mineral (especially calcium) sources. The absence of any one of these is an immediate indication that the diet should be evaluated further.

Protein and Amino Acids

When evaluating the dietary source of protein and amino acids, it is important to consider a multitude of factors. Is the protein source of animal or plant origin? Animal-based protein sources are recommended for both dogs and cats due to their pattern of essential amino acids. However, it is not unusual to see plant proteins as the major or sole protein source in a canine diet. Plant proteins can be used for feline diets but are not recommended by these authors as it is often difficult to meet the cat's nitrogen and amino acid requirements using plant proteins, and diet palatability is often poor. Plant proteins are also frequently limiting in the essential amino acids methionine, lysine, and tryptophan.

Most plant proteins do not contain taurine, an essential amino acid for cats, and under some circumstances possibly a conditionally essential amino acid in dogs. Even when animal-based protein sources are used, these authors prefer to see supplemental taurine in every feline diet.

The taurine content in animal proteins can vary significantly, with muscle generally containing less taurine than organ meats (Spitze et al. 2003). Cooking also influences taurine concentrations, and it can be lost to a significant extent when using cooking methods that expose proteins to water, thereby leaching the taurine from the food (Spitze et al. 2003). These findings imply that if one does not cook the protein source, taurine deficiency is less of a concern; however, the literature does not support this thinking. Taurine deficiency has been recognized in cats that consume home-prepared diets using raw protein. One research update reported dilated cardiomyopathy associated with taurine deficiency in a group of growing cats fed a diet consisting solely of ground raw rabbit (Glasgow et al. 2011). A second study evaluated plasma taurine concentrations in sand cats (*Felis margarita*) fed either a commercial feline kibble or a raw food diet (Crissey et al. 1997). Despite a 15% increase in digestibility and a 40% increase in taurine content compared to the kibble diet, cats consuming the raw food diet had significantly lower plasma taurine concentrations. Although the plasma taurine concentrations were not below the point at which clinical taurine deficiency would be seen, they were reduced by approximately 25% during the 12-day study period. While arguably this is a crude estimate at best, if one were to project the continued rate of decline, plasma taurine would fall below the concentration where the clinical signs of taurine deficiency are frequently noted at approximately day 20 of raw food consumption. These effects would likely be more pronounced under the conditions of a more demanding life stage than maintenance, such as during growth or reproduction.

The exact mechanism of how raw diets can potentiate taurine deficiency is unknown at this time. The amount of

taurine available to the cat from its diet is dependent upon a number of factors including the quality and quantity of dietary protein, as well as how that protein is processed (Hickman et al. 1990; Backus et al. 1994; Kim et al. 1996a, 1996b). These factors in turn influence gastrointestinal microbial numbers and/or species that can cause taurine loss by accelerating turnover of bile acids conjugated with taurine and decrease recycling of taurine by the enterohepatic route. These factors may influence changes in bacteria that favor those populations that degrade taurine. In addition to these factors, low levels of vitamin E in a diet can cause meat to lose taurine when it is processed and ground (Lambert et al. 2001).

Specific recommendations should be provided regarding the cut and fat content of the protein source for animal proteins. The fat content of a diet can vary considerably if different cuts of meat or poultry are used. The inclusion or absence of skin should be noted in the recipe and if using ground meat or ground poultry, the percentage of fat in the product should be specified.

Fatty Acids

Dogs and cats require linoleic acid (18:2 n-6) (NRC 2006). While animal fats contain some linoleic acid, an additional source is often necessary to meet the pet's requirement. Many common vegetable oils can be used as a dietary source of linoleic acid including corn, safflower, sunflower, and soybean oil. Corn oil has the highest concentration of linoleic acid so it is needed in the least amount to meet the requirement. This can be very helpful if one is trying to limit the overall amount of fat in the diet. Many owners want to use olive oil since they are using it in their own diets to combat coronary artery disease. However, while olive oil is high in monounsaturated fatty acids, it is a poor source of linoleic acid, thereby requiring large amounts to meet the animal's requirement. In addition, dogs and cats do not develop clinically significant atherosclerosis leading to myocardial infarctions and death, likely due to differences in lipoproteins and life span compared to humans. Therefore, its use is not recommended. Cats also require arachidonic acid, found in high concentrations in animal fats and not in vegetable-based fats. This adds another layer of complexity in trying to meet the nutrient requirements of cats using vegetarian diets. Borage, black currant, and evening primrose oils may be used, as these can supply gamma linolenic acid, a precursor for arachidonic acid.

Emerging evidence suggests that omega-3 fatty acids may provide some health benefits to dogs and cats, especially during growth and development (Bauer 2006). Specifically, benefits may be derived from docosahexaenoic (DHA, 22:5 n-3) and eicosapentaenoic (EPA, 20:5 n-3) acids. While alpha-linolenic acid (18:3 n-3) is often supplied in products by ingredients such as flaxseed or canola oil, dogs and cats cannot efficiently convert alpha-linolenic acid to EPA and DHA, so fish, krill, or algal oil sources are required (NRC 2006).

Carbohydrates

While carbohydrates are not required in dogs and cats (NRC 2006), one should note their presence or absence in the diet. Their absence, while not nutritionally essential, is noteworthy as the diet will then be one that is high in protein and/or fat. There are four carbohydrate groups from a functional perspective: absorbable (monosaccharides); digestible (disaccharides, certain oligosaccharides, and nonstructural polysaccharides); fermentable (lactose, certain oligosaccharides, dietary fiber, and resistant starch); and nonfermentable (certain dietary fibers) carbohydrates (NRC 2006). While many view carbohydrates negatively (especially those in the absorbable and digestible categories) due to their high digestible starch content and the belief that such products are bad for dogs and cats (unsubstantiated scientifically), they often overlook the other nutrients supplied. For example, oatmeal can supply a significant amount of protein and fat to a diet. Carbohydrates also provide fermentable and nonfermentable carbohydrates in the form of dietary fiber. Soluble fibers are generally better energy substrates for gastrointestinal microorganisms than insoluble fibers due to their increased rate and extent of fermentation (NRC 2006). Prebiotics are one form of soluble fiber that may stimulate the growth and well-being of bacteria in the gastrointestinal tract thereby supporting overall health.

Vitamin and Mineral Supplements

An obvious vitamin and mineral supplement should be readily apparent in every recipe. Many owners prefer to try to address their pet's vitamin and mineral needs using whole foods such as liver or bone rather than a manufactured supplement. Such an approach is very difficult to do and can heighten the risk of a nutritional deficiency or excess in the diet. Natural foods have tremendous variability in their vitamin and mineral content based on how and where the food source was raised, feeding or fertilizing methods, part of the animal or plant used, and how the source is prepared. For these reasons, the authors recommend using a distinct vitamin and mineral supplement.

Some veterinary nutritionists and owners prefer to use an all-in-one veterinary supplement [Balance IT, founded

by one of the authors (SJD)], which limits the number of ingredients added to the diet, whereas others prefer to use supplements designed for the human market to meet the vitamin and mineral needs of the patient. With this approach the number of ingredients that must be measured and added to the diet will increase significantly. This approach generally necessitates a calcium/phosphorus supplement; a multivitamin/multimineral supplement; a taurine supplement (for cats and occasionally dogs); iodized salt or light salt to provide iodine, sodium, potassium, and chloride; choline if methionine is limiting in the diet (i.e., vegetarian diets); and then often additional zinc and/or vitamin B12, as many human vitamin/mineral supplements have lower levels of these nutrients. In some cases, however, this latter approach must be used if additional nutrient restriction is required beyond what an all-in-one veterinary supplement provides due to an underlying disease process. A common example includes dogs with chronic kidney disease requiring potassium restriction secondary to life-threatening hyperkalemia (Segev et al. 2010).

General Considerations

After reviewing the recipe for nutrient categories and specific ingredients, consideration should be given to the calories the recipe provides on a daily basis as well as the percentage of calories coming from each of the major nutrients: protein, fat, and carbohydrate. Home-prepared diets can be very energy dense depending on their ingredient composition. They are highly digestible in most cases and very palatable. This combination can predispose animals that consume them to weight gain and obesity if they are receiving too many calories a day and not being closely monitored. The percentage of calories coming from protein, fat, and carbohydrate should be considered in light of the animal's signalment and health status. It is important that the nutrient distribution be appropriate if an animal is receiving a home-prepared diet to manage a disease. In some cases, this may also include the micronutrients. For example, in an animal with renal disease, one is not only concerned about the protein content but also phosphorus, sodium, and potassium. In the authors' experience if a recipe has not been formulated by a board-certified veterinary nutritionist, it is often very difficult to determine the calorie content, the percentage of calories supplied by protein, fat, and carbohydrate, and the micronutrient composition. The absence of any of this information is an indicator that the diet should be evaluated further.

One should inspect the recipe with regard to the instructions. In the ingredient list it should specify if units of measure are of cooked or raw material. Specifying gram units in addition to traditional volume measures (i.e., cups or teaspoons) is very helpful because often the required amounts of some nutrients fall outside or below the units available on common measuring equipment in the average kitchen. The authors recommend that owners who wish to home prepare their pets' diets purchase a kitchen scale, as weighing the ingredients is much more accurate that volume measures. Very clear cooking instructions and ingredient preparation guidelines should be provided. For example: Should the meat be pan fried (with or without added fat), baked, boiled, or braised? How should the rice be prepared (with or without added salt)? Should the skin be left on potatoes?

Specific brand names should be provided with respect to vitamin and mineral supplements as there is tremendous variability in the market with regard to the nutrient content and amounts provided in such products. Furthermore it is not uncommon for many recipes to simply state "add a vitamin and mineral supplement to meet the patient's requirements." Such guidelines are very poor advice as they provide no information and require that an owner with no nutritional training decide what supplement to give and how much. Guidelines with respect to how the supplements are added and handled should also be provided. Many vitamins can be destroyed by heating, which can occur if added during the cooking process.

Lastly, because many owners like to prepare their pet's food in large batches, it is very helpful if instructions are provided for them to do so. How and when should vitamin and mineral supplements be added to batches? Can the batch of food be refrigerated or frozen? In some cases, defrosting and reheating instructions may be necessary as well.

Many veterinary practitioners successfully use home-prepared diets in the management of their patients. It is important to obtain home-prepared diet recipes from reputable sources, formulated by properly trained individuals. While there are a number of recipes in the veterinary literature, in textbooks, and referred publications, studies suggest that they may not always be nutritionally adequate (Lauten et al. 2005). Be extremely cautious of recipes obtained from the Internet, or publications designed for use by the general public. A better option is to have a diet specially formulated for one's patient or formulate one for one's patient using commercially available formulation software [e.g., balanceit.com, which was founded by one of the authors (SJD)], creativeformulation.com, esha.com, feedsoft.com, format-international.com, and Mixit-Win (Tel: 619-226-7900). A custom-formulated diet accounts

for the patient's specific needs and medical problems, using ingredients the pet likes. Contact the veterinary teaching college in one's area to see if their clinical nutritionist provides this service. There are also a number of veterinary nutritionists in the private sector who will custom formulate diets. Board-certified veterinary nutritionists may be located through the American College of Veterinary Nutrition (AVCN) at www.acvn.org.

Assessment While on a Home-Prepared Diet

It is recommended that any pet receiving a home-prepared diet be checked by a veterinarian at least every 6 months (animals with a concurrent medical condition may need to be seen more frequently as indicated by their problem). The physical examination should include an assessment of body condition, body weight, and if indicated, diagnostic tests such as blood work and urinalysis. A retinal examination should be performed on every cat. This visit also allows the inclusion of specific diagnostic tests to determine how well the patient is responding to its medical and/or nutritional management.

The patient's diet history should also be updated at every visit; this will help alert the practitioner to any changes in the prescribed recipe. It can also be helpful to have the owner provide a diet record of exactly how much and what the animal ate for the past week. If changes from the prescribed feeding plan are noted, often occurring in the form of ingredient substitutions (referred to as "diet drift") or the exclusion of an ingredient (often the vitamin and mineral supplements), it is important to determine why the client implemented these changes. In some cases, the owner may simply not understand the importance of the ingredient. Often what may appear to be a simple substitution can drastically alter the nutrient profile of the diet. In animals with an underlying medical condition, such innocent adjustments may potentiate advancement of their pet's disease. In other cases, perhaps the patient does not find the diet to be palatable. The pet may also be having an adverse response to the formulation or one of the ingredients, or it may be experiencing a progression of its disease process. Recheck visits allow the practitioner to educate the owner, make adjustments, or pursue a reformulation of the diet if needed.

RAW FOOD FEEDING

Concerns regarding nutritional adequacy not only apply to home-prepared raw diets but to commercial raw diets as well. One study that looked at the nutritional adequacy of home-prepared raw food also looked at the nutritional adequacy of several commercial raw food diets (Freeman and Michel 2001). Both commercial raw diets had nutrient concentrations that fell below minimum AAFCO recommendations. Similarly, clinical case reports of problems in animals consuming commercial raw food diets are now beginning to appear in the literature (Taylor et al. 2009). Commercially produced raw diets fall under the same AAFCO labeling guidelines with respect to reporting nutrient content, ingredients, and nutritional adequacy statements. AAFCO recommendations for nutrient minimums and maximums exist to guide and protect against nutritional concerns in commercially produced foods. While some of these recommendations are based on studies using semi-purified diets, there are also many studies using extruded or moist diets. On the other hand, there is a paucity of data concerning nutritional requirements, bioavailability, and the effect of raw food on gastrointestinal microbial populations in dogs and cats. It is well known that nutrient requirements can vary depending on the type of diet (i.e., taurine requirements are almost double for canned products compared to extruded diets). Therefore, one can speculate that similar examples may exist for dogs and cats that consume raw diets and that further research is needed.

There are concerns that the consumption of bones can cause oral and dental trauma as well as esophageal and gastrointestinal foreign bodies. The use of raw bones (compared to cooked) may reduce the risk of splintering and tooth fractures, but sharp fragments can still occur and puncture the mucosa at any point along the gastrointestinal route. Grinding bones may help reduce the risk of trauma and obstruction, but the availability of the calcium from these sources is unknown (see Box 8.1).

The veterinarian's job is not only to care for the health and well-being of their animal patients but also those who are the guardians of these pets as well. From this perspective concerns regarding pathogenic bacteria in raw diets and subsequent environmental contamination are paramount.

There is growing evidence to support these concerns. Evidence for the possible transmission of food-borne pathogenic bacteria from dogs to humans exists (Gutman et al. 1973; Morse et al. 1976; Sato et al. 2000). In Alberta, Canada, 9 of 12 case patients with *S. infantis* infection had been exposed to pig ear treats, and *S. infantis* was isolated from a pig ear treat collected from one of the case patients. The isolate recovered from the pig ear was indistinguishable from *S. infantis* isolates recovered from fecal samples obtained from humans with salmonellosis (Laboratory Centre for Disease Control 2000; Finley, Reid-Smith et al. 2006).

Potential human pathogens have been isolated in both commercial and home-prepared raw diets (Chengappa et al. 1993; Freeman and Michel 2001; Joffe and Schlesinger 2002; Weese et al. 2005; Strohmeyer et al. 2006; Leonard et al. 2010). Animals fed raw diets have been reported to shed the same viable organisms that were isolated in their food (Finley, Ribble et al. 2007). There have been reports of racing Greyhounds, sled dogs, guard dogs, and cats with *Salmonella* infections due to consumption of contaminated raw meat (Caraway et al. 1959; Cantor et al. 1997; Stone et al. 1993; Stiver et al. 2003; Morley et al. 2006).

Arguably, while many animals never become ill while consuming raw food diets, they still pose a risk to humans and other animals through environmental shedding (Finley, Reid-Smith et al. 2006; Finely, Ribble et al. 2007). Individuals preparing raw diets are also at risk by handling contaminated meat and egg products. Those greatest at risk are the very young and old, in addition to the immunocompromised.

There is no documented evidence that feeding raw meat has any health or nutritional advantages over cooked foods. The FDA does not advocate the feeding of raw meat, poultry or seafood to pets (FDA 2007). However, recognizing that some owners will continue this practice, they provide a set of recommendations regarding the safe handling of raw foods for pet owners to follow.

As veterinarians, it is important to discuss with owners the risks associated with feeding raw diets not only to the pet but also to those who share the environment with that animal. In many cases, safer alternatives can be offered that will often address the underlying motivations that lead the owner to try this feeding approach initially. There are numerous commercial diets on the market that provide similar nutrient profiles to raw diets or do not contain grains or offer natural ingredients and preservatives. If the owner still wishes to prepare food at home, a home-prepared, cooked diet formulated by a trained nutritionist is an excellent option.

In some cases, despite understanding all of the risks, an owner may wish to continue to feed a raw diet. Practitioners should refer their clients to the FDA's website and go over safe handling and preparation of food, as well as cleaning practices. It has been shown that simple routine washing may not be enough to eliminate potential food-borne pathogens in the pet's food bowl and environment (Weese and Rousseau 2006). It is also important to document any discussions one has on this subject, as it may have legal ramifications (LeJeune and Hancock 2001).

SUMMARY

- Each type of commercial pet food—dry, moist, semi-moist, and raw—has potential advantages and disadvantages. It is important for the practitioner to understand these in order to recommend the best diet to their patient.
- There are good quality commercial diets in every segment of the market, and the price of a pet food does not always equate with the quality of the diet.
- The major indication for placing an animal on a home-prepared diet is a medical condition that requires special nutritional modifications not addressed in a commercial or veterinary therapeutic diet.
- All home-prepared diet recipes should be reviewed by the practitioner and entered into the patient's medical record. Recipes that are obtained from books, lay publications, or the Internet should be evaluated by a veterinary nutritionist or the practitioner using evaluation software for adequacy.
- Raw food diets pose many potential risks including nutritional excesses or deficiencies, dental injury, gastrointestinal obstructions and perforations, bacterial contamination, and other zoonotic diseases. Clients should be educated by their veterinarian with respect to these risks.

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Nutritional Management of Body Weight

9

Kathryn E. Michel

KEY POINTS

- Many companion animals are overweight or obese.
- Overweightedness and obesity are associated with increased risk of disease and reduced life span in dogs and cats.
- Caregivers should be taught body condition scoring and how to use this technique to adjust their pets' caloric intake.
- Key elements for ensuring the success of a weight reduction program are obtaining a thorough dietary history, tailoring the program to the patient, and scheduling regular recheck visits to monitor the patient's progress and adjust the plan as necessary based on response.

INTRODUCTION

Animals become overweight as a consequence of maintaining a state of positive energy balance; that is to say, they consume calories in excess of their caloric expenditure. Weight gain can be rapid if the caloric excess is large. However, even a modest chronic excess in caloric intake can result in significant weight gain over the long term. For example, a cat that consumes a mere 10 kilocalories above its daily energy requirement every day will accumulate about a pound of adipose tissue in the course of a year. For the typical domestic shorthaired cat, that would be equivalent to 10% of its ideal weight, not at all an insignificant weight gain.

Obesity has been defined as an accumulation of excessive energy storage in the form of adipose tissue sufficient to contribute to disease (National Institutes of Health 1985). Both the condition of overweightedness and obesity have been clearly defined for humans using anthropometric criteria. Epidemiological data from the past few decades has revealed that increasing numbers of people in developed and developing regions of the world are overweight or obese (Silventoinen et al. 2004; Ogden et al. 2006). The impact of overweightedness and obesity on human health has also been extensively investigated, and it is estimated that in the United States alone these conditions result in over $70 billion in direct health-care costs each year (Colditz 1999).

There seems to be general agreement that excess weight gain is the most common nutrition-related disorder seen in companion animals today. While compared to human studies there have been relatively few large investigations of the prevalence of overweightedness and obesity in pet dogs and cats, estimates range from 24% to 44% of the adult population (Edney and Smith 1986; Scarlett and Donoghue 1996; Lund et al. 2005; Lund et al. 2006). The survey of the body condition of pet dogs and cats that examined the largest and most geographically diverse cohort obtained body condition scores from private veterinary practices throughout the United States. These investigators found that 28.7% of 8,159 adult cats were classified as overweight and 6.4% as obese (Lund et al. 2005). Of 21,754 dogs seen at these same practices, 29.0% were deemed overweight and 5.1% obese (Lund et al. 2006). When the data for only middle-aged pets (between the ages of 5 and 11 years) were analyzed, 44% of the cats and 42% of the dogs were scored as overweight or obese,

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percentages that approach those reported for people living in the United States (Lund et al. 2005; Lund et al. 2006; Ogden et al. 2006).

THE HEALTH CONSEQUENCES OF OVERWEIGHTEDNESS AND OBESITY

In comparison to the scientific literature regarding the adverse effects of excess weight gain on human health, our knowledge of the impact of this condition on the health of pet dogs and cats is limited. Not too long ago the potential sequelae of weight gain, as discussed in the veterinary literature, were mostly matters of speculation based on data from human patients. However, there are now a number of published investigations that document an association between overweightedness and obesity and increased risk of disease and decreased longevity in both cats and dogs. The best evidence to date documents the association between obesity and orthopedic disease in dogs, and between obesity and diabetes mellitus in cats.

Obesity as a Risk Factor for Canine Orthopedic Disease

One of the first large-scale epidemiological studies on overweightedness and obesity in dogs was performed in the United Kingdom, and it found that 2.9% of a sample of 8,268 dogs seen at 11 different veterinary clinics were classified as grossly overweight (Edney and Smith 1986). This subset of dogs had an increased prevalence of circulatory and articular/locomotor diseases. However, this finding was confounded by the fact that in this population these disorders were also highly associated with old age.

In a 14-year longitudinal study of pair-fed Labrador Retriever littermates, one member of the pair was fed 25% less food than the other throughout life (Kealy et al. 2002). On average the limit-fed dogs maintained an optimal body condition score (4.6 ± 0.2/9) while their respective full-fed pairs were moderately overweight (6.7 ± 0.2/9). Significantly fewer of the limit-fed dogs developed osteoarthritis than the full-fed dogs, and those that did had less severe disease with a later onset in life. This finding was particularly dramatic in light of the relatively modest difference in body condition between the limit-fed and full-fed dogs.

There is also evidence that overweight dogs with preexisting orthopedic disease benefit from weight loss. One prospective study found that when nine pet dogs with radiographic and clinical signs of coxofemoral joint osteoarthritis underwent a successful weight reduction program, all dogs experienced a significant decrease in severity of clinical signs based on subjective evaluation (Impellizeri et al. 2000). Other investigations of the impact of weight loss on dogs with documented osteoarthritis have reported similar findings with dogs showing significant improvement of lameness as documented by force plate and kinetic gait analysis after a successful weight loss program (Burkholder et al. 2001; Marshall et al. 2010).

Obesity as a Risk Factor for Feline Diabetes Mellitus

The association between obesity and Type II diabetes mellitus in people is well documented (Hu et al. 2001). Obesity promotes insulin resistance, which in turn leads to increased insulin secretion by the pancreatic beta cells, with the consequence over time of beta cell destruction through one or more proposed mechanisms, including islet amylin deposition, beta cell exhaustion, and glucose toxicity (Rossetti et al. 1990). Abnormal insulin secretion and abnormal glucose tolerance have been documented in both overweight dogs and cats. Both species have been shown to develop glucose intolerance and hyperinsulinemia with weight gain that resolves if the animal returns to normal body condition (Mattheeuws et al. 1984; Fettman et al. 1998). The form of diabetes that affects the majority of dogs most closely resembles human type I diabetes. Feline diabetes mellitus, however, resembles human type II diabetes in several key respects including islet amylin deposition and an association with an overweight body condition (Yano et al. 1981; Panciera et al. 1990). One investigation found that overweight cats had a fourfold greater risk of becoming diabetic than normal weight cats (Scarlett and Donoghue 1998).

Additional Health Risks of Obesity in Dogs and Cats

Other investigations have shown excess body weight to be a risk factor for a number of other health problems seen in companion animals. Overweight cats have been found to be at greater risk for lower urinary tract diseases, nonallergic dermatitis, oral disease, lameness, and feline idiopathic hepatic lipidosis (Burrows et al. 1981; Scarlett and Donoghue 1998; Lund et al. 2005). Overweight dogs have been found to be at increased risk for pancreatitis and renal pathology (Hess et al. 1999; Finco et al. 2001). There is also epidemiological evidence that neoplasia is associated with an overweight body condition in both dogs and cats (Lund et al. 2005; Lund et al. 2006) although a more recent study showed that any such association in dogs is likely cancer type specific (Weeth et al. 2007). In general, obesity can compromise an animal's ventilatory capacity ("Pickwickian Syndrome") and thus affect tolerance of exercise, heat, and anesthesia.

It has become increasingly evident that adipose tissue, long viewed simply as an energy depot, actively produces both hormones that are involved in energy homeostasis (e.g., leptin and resistin) and cytokines, some of which are important modulators of inflammation (e.g., TNF-alpha, IL-1) (Miller et al. 1998; Gayet et al. 2004). Consequently, obesity is now recognized as a state of chronic low-grade inflammation, a condition that may prove to play a role in the pathogenesis of some of the diseases for which overweight individuals are at risk, including osteoarthritis and diabetes mellitus.

As previously noted there is evidence that overweight dogs and cats experience decreased longevity. In the study involving the pair-fed Labrador Retrievers, a significant difference in median life span was found: 13 years for the limit-fed dogs compared to 11.2 years for the control full-fed dogs (Kealy et al. 2002). With regard to cats, in an investigation of over 2,000 adult cats seen at veterinary clinics in the mid-Atlantic region of the United States, multivariate statistical analysis controlled for age found that middle-aged obese cats had greater risk of mortality than cats at optimal body weight (Scarlett and Donoghue 1996).

INCREASING AWARENESS OF OVERWEIGHTEDNESS AND OBESITY

Given the evidence that excessive weight gain can have significant health consequences for pet dogs and cats, why are so many pets overweight? Since most pets do not obtain food on their own, it would seem a relatively simple task for the caregiver to feed a pet so that it did not gain excess weight. In order to do this, however, the caregiver must be able to distinguish what constitutes an optimal weight for the pet.

Targeting Optimal Weight

Basing a pet's feeding management on maintaining a target body weight has disadvantages, particularly in the case of dogs. Weight tables similar to available human height-weight tables would be impractical and difficult to develop for dogs and cats due to the variation in conformation among and within breeds and the large number of mixed breed pets. Furthermore, most people do not have ready access to an accurate scale that would accommodate a dog or a cat. There have been attempts to develop zoometric techniques for dogs and cats similar to the anthropometric techniques used in humans (Stanton et al. 1992). However, while these techniques might be useful in a research setting, they are again impractical as a means of assessing a pet on a day-to-day basis. Body condition scoring, on the other hand, requires no special equipment, is simple to learn, and can be used to assess and modify feeding practices in the home setting.

Body Condition Scoring

Several different scoring systems for dogs and cats have been developed. A 9-point system is described in Tables 9.1 and 9.2 and illustrated in Figs. 9.1 and 9.2. Applying the system involves both visual assessment of the pet and palpation to assess body fat over the ribs, abdomen, lumbar area, and tail base. The combination of the description and illustrations clarifies the distinctions between scores and makes the system simple to apply. This system has been validated for use with dogs and cats both in terms of reproducibility between trained observers and body composition as measured by dual energy x-ray absorptiometry (Laflamme 1997a, 1997b). Each increment in body condition score (BCS) is approximately equivalent to 10% to 15% additional weight due to body fat. A score of 4 to 5 is considered optimal for dogs and reflects a body fat level of 15–20%. For cats, a BCS of 5 is considered optimal and in this species reflects a level of 25–30% body fat.

In practice, once a person was familiarized with the system and was able to recognize what constituted ideal body condition, they could use it to adjust how their pet was fed. The caregiver would assess the pet's BCS on a routine basis (such as monthly) and increase or decrease accordingly the amount of food offered the pet. However, despite the simplicity of this approach, several studies have found that people's perception of their pet's body condition is often at odds with the assessment of a trained observer. Most investigations suggest that people are likely to underestimate their pet's BCS. A study involving 201 dogs found that while the expert scored 79% of the dogs as overweight or obese, only 28% of the caregivers scored their dogs above ideal (Singh et al. 2002). Another study, which looked at cats living in New Zealand, found that, overall, people underestimated their cat's BCS only 25% of the time; however, people underestimated BCS in 60% of the cats that were overweight or obese (Allan et al. 2000).

This misperception is compounded if the attending veterinarian neglects to identify and call attention to overweight and obese patients. In a large survey of U.S. veterinary practices, approximately 28% of the canine and feline patients were scored as overweight or obese, but only 2% had weight recorded as an issue (Lund et al. 1999). The best practice is to record a body weight and a BCS for each patient on every visit. The BCS puts the body weight in context for monitoring trends and is useful

Table 9.1. The 9-Point Body Condition Scoring System for Dogs*

Too Thin	
1	Ribs, lumbar vertebrae, pelvic bones and all bony prominences evident from a distance; no discernible body fat; obvious loss of muscle mass.
2	Ribs, lumbar vertebrae, and pelvic bones easily visible; no palpable fat; some evidence of other bony prominence; minimal loss of muscle mass.
3	Ribs easily palpated and may be visible with no palpable fat; tops of lumbar vertebrae visible; pelvic bones becoming prominent; obvious waist and abdominal tuck.
Ideal	
4	Ribs easily palpable, with minimal fat covering; waist easily noted, viewed from above; abdomen tucked up when viewed from side.
5	Ribs palpable without excess fat covering; waist observed behind ribs when viewed from above; abdomen tucked up when viewed from side.
Too Heavy	
6	Ribs palpable with slight excess fat covering; waist is discernible viewed from above but is not prominent; abdominal tuck apparent.
7	Ribs palpable with difficulty; heavy fat cover; noticeable fat deposits over lumbar area and base of tail; waist absent or barely visible; abdominal tuck may be present.
8	Ribs not palpable under very heavy fat cover, or palpable only with significant pressure; heavy fat deposits over lumbar area and base of tail; waist absent; no abdominal tuck; obvious abdominal distention may be present.
9	Massive fat deposits over thorax, spine, and base of tail; waist and abdominal tuck absent; fat deposits on neck and limbs; obvious abdominal distention.

*Reprinted with permission from the Nestlé Purina PetCare Company.

when more than one clinician is caring for the patient. Scoring body condition during an office visit also provides opportunities to ensure that the pet's caregiver is properly instructed in this technique and to initiate a discussion about weight control when indicated.

Understanding the Risk Factors for Weight Gain

There are many aspects of how companion animals are housed and fed that can predispose a dog or cat to weight gain. Recognizing these risks and educating the pet's caregiver could help prevent a pet from becoming overweight in the first place.

Several studies have implicated feeding calorically dense commercial foods as a contributing factor for weight gain in cats (Robertson 1999; Scarlett et al. 1994; Lund et al. 2005). Interestingly, the studies that have looked at frequency of feeding (free choice vs. meal fed) have not found this factor to be associated with risk for becoming overweight, although clearly pets that are fed free choice are at liberty to consume excess calories, particularly when they are fed energy-dense, palatable foods (Robertson 1999; Allan et al. 2000).

Lack of exercise has also been cited as a contributing factor in obesity for humans and pets alike (Colditz 1999; Robertson 1999; Scarlett et al. 1994; Lund et al. 2005). The physical environment where increasing numbers of people, along with their pets, are residing lacks the space and infrastructure (e.g., parks, sidewalks) to facilitate physical activity. Many cats, and increasingly some dogs, are confined indoors. Many dogs rely on a caregiver to exercise them by leash walking or taking them to a protected open space to run, endeavors that require time and commitment on the part of the caregiver.

Another major contributing factor for weight gain in companion animals is neutering. A number of investigations have shown that neutering can affect feline and canine energy balance (Root et al. 1996; Fettman et al. 1998; Hoenig and Ferguson 2002; Kanchuk et al. 2003; Jeusette et al. 2006). Upon neutering, cats will increase food intake within days of the procedure. There is also some evidence to suggest that neutering results in a decrease in energy requirements, although when energy expenditure is normalized to lean body mass (as opposed to total body weight) this does not appear to be the case

Table 9.2. The 9-Point Body Condition Scoring System for Cats*

Too Thin	
1	Ribs visible on shorthaired cats; no palpable fat; severe abdominal tuck; lumbar vertebrae and wings of the ilia easily palpated.
2	Ribs easily visible on shorthaired cats; lumbar vertebrae obvious with minimal muscle mass; pronounced abdominal tuck; no palpable fat.
3	Ribs easily palpable with minimal fat covering; lumbar vertebrae obvious; obvious waist behind ribs; minimal abdominal fat.
4	Ribs palpable with minimal fat covering; noticeable waist behind ribs; slight abdominal tuck; abdominal fat pad absent.
Ideal	
5	Well-proportioned; observe waist behind ribs; ribs palpable with slight fat covering; abdominal fat pad minimal.
Too Heavy	
6	Ribs palpable with slight excess fat covering; waist and abdominal fat pad distinguishable but not obvious; abdominal tuck absent.
7	Ribs not easily palpable with moderate fat cover; waist poorly discernible; obvious rounding of abdomen; moderate abdominal fat pad.
8	Ribs not palpable with excess fat covering; waist absent; obvious rounding of abdomen with prominent abdominal fat pad; fat deposits present over lumbar area.
9	Ribs not palpable under heavy fat cover; heavy fat deposits over lumbar area, face, and limbs; distention of abdomen with no waist; extensive abdominal fat deposits.

*Reprinted with permission from the Nestlé Purina PetCare Company.

(Kanchuk et al. 2003). Supporting these findings, which implicate neutering as a factor predisposing to weight gain, are the epidemiological studies that have found neutered dogs and cats to be at greater risk of being overweight or obese (Edney and Smith 1986; Scarlett et al. 1994; Lund et al. 2005; McGreevy et al. 2005; Lund et al. 2006; Weeth et al. 2007).

ACCURATE ACCOUNTING OF CALORIC INTAKE

The first step for developing a weight loss program is to perform a complete physical exam and obtain a thorough dietary history. The physical exam findings will help identify any underlying conditions that may have contributed to the weight gain, or that may need to be taken into account when formulating the weight loss plan, such as conditions that could limit the pet's ability to exercise. It will also verify that the pet's weight gain is indeed attributable to an increase in adiposity and not another condition such as ascites. The physical exam may prompt further diagnostic testing for conditions that could predispose to weight gain including hypothyroidism or hyperadrenocorticism. While it is likely that a minority of overweight pets have an underlying endocrinopathy, it will be necessary to diagnose those cases and manage them appropriately in order to have success with the weight loss program.

An absolutely key step for formulating a successful weight loss plan is performing a thorough dietary history (see Box 9.1).

This process has several objectives, the first of which is to obtain an accurate accounting of all foods fed to a pet on a typical day. However, a properly executed diet history goes beyond simply counting up calories. This will be an opportunity to evaluate all the ways that food is involved in interactions between the pet and the other members of its household. This is also when the pet's caregivers should be given the opportunity to offer their viewpoints regarding the pet's need for weight loss and the proposition of modifying their feeding practices. It has to be absolutely clear from the start that the caregivers perceive that the pet is overweight, that they understand why weight loss is being recommended for their pet and that they are willing to address the problem. Thus, in addition to detailing what and how much the pet is being fed, the dietary history will also reveal potential pitfalls and obstacles in advance and allow the weight loss plan to be tailored to the individual's

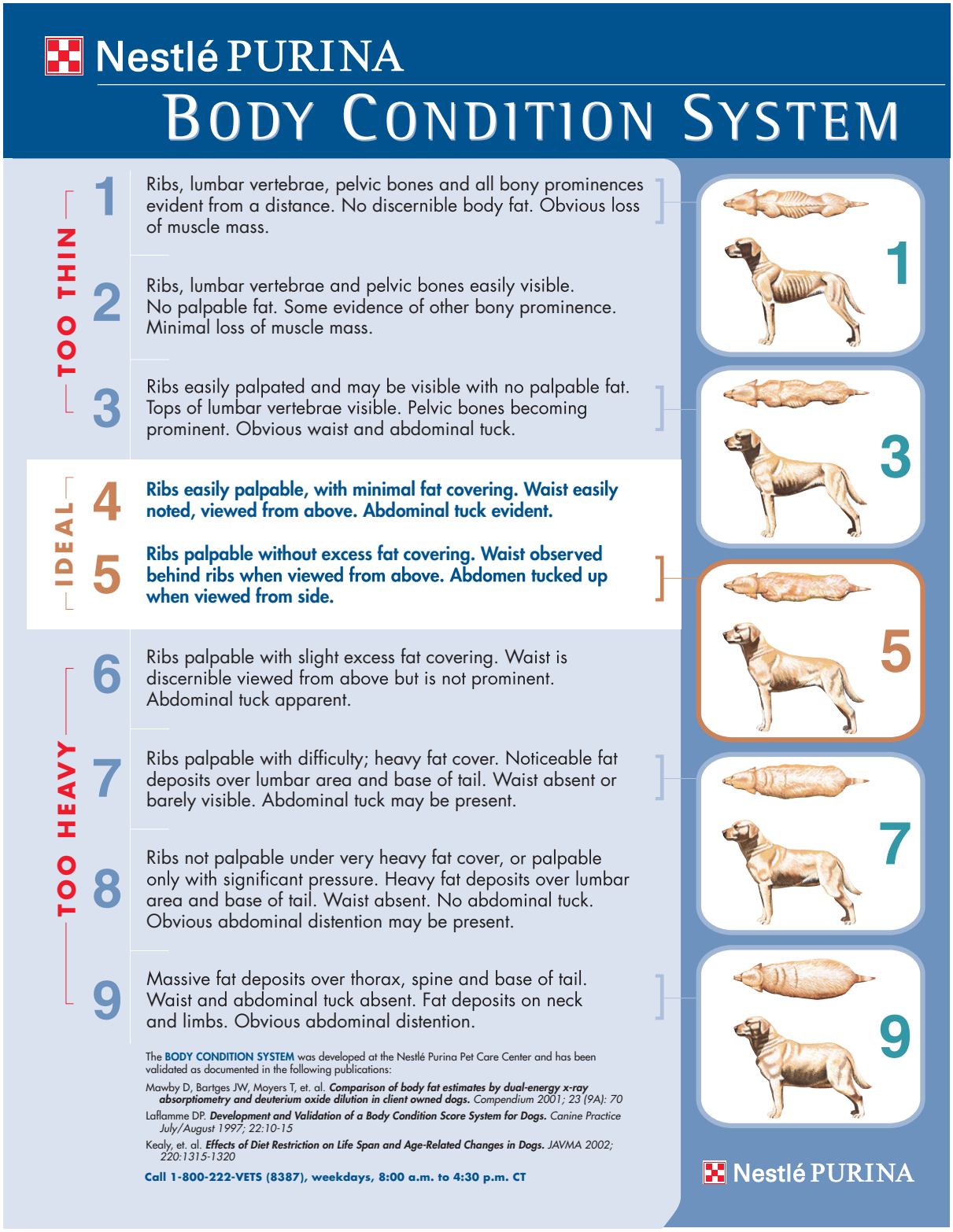

Fig. 9.1. Illustration of the 9-point body condition scoring system for dogs (used with permission from Nestlé Purina PetCare Company).

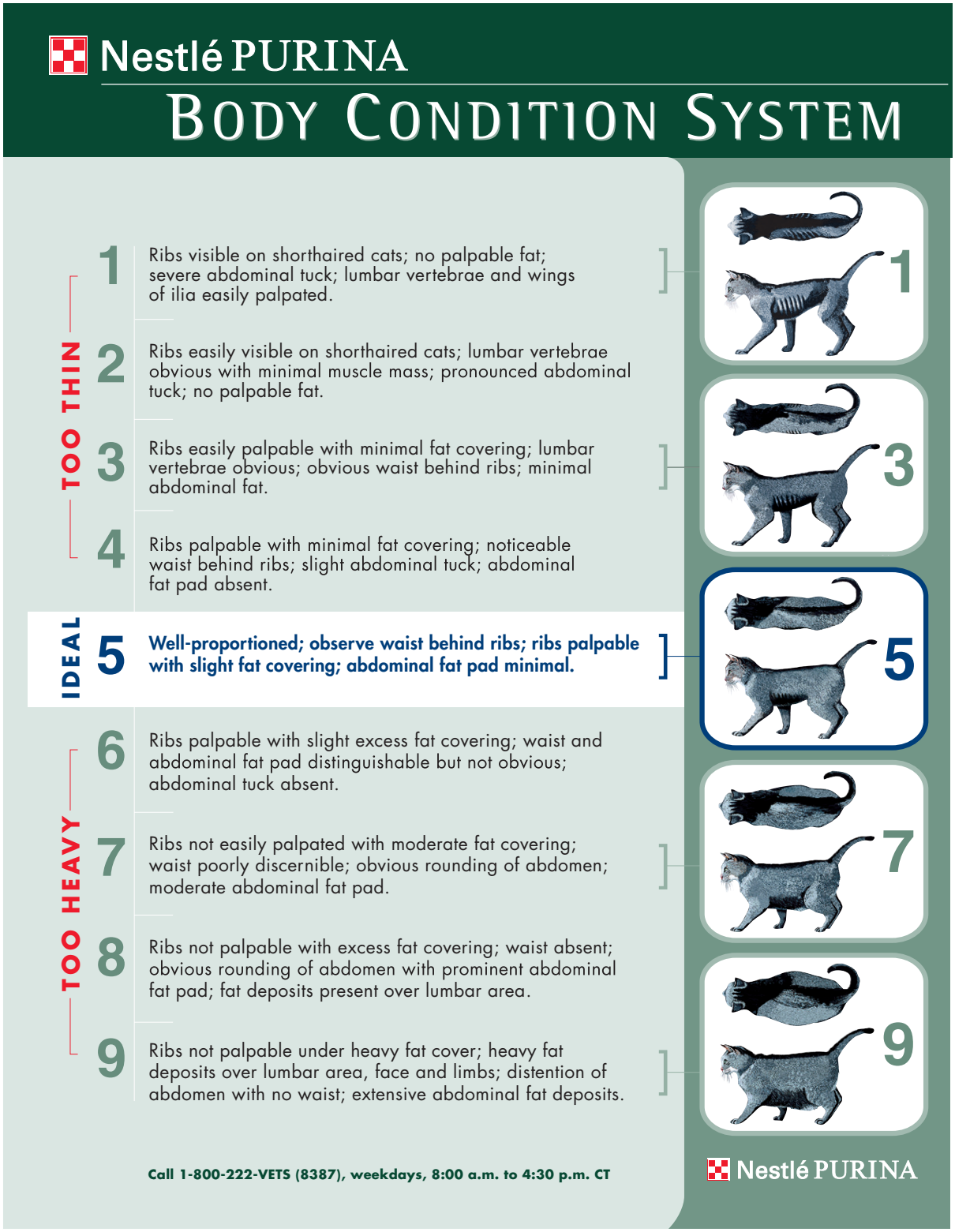

Fig. 9.2. Illustration of the 9-point body condition scoring system for cats (used with permission from Nestlé Purina PetCare Company).

BOX 9.1. CHECKLIST FOR A DIET HISTORY.

- Who lives in the household?
  - People
  - Other pets
- Who feeds the pet?
- How is the pet fed?
  - Free choice vs. meals
  - How is the fed portion measured?
  - What is the pet's feeding behavior?
  - Can the pet hunt or scavenge for food?
- What is fed?
  - Specific varieties and amounts of commercial pet foods
  - Table foods or scraps
  - Home-prepared diets
  - Treats
  - Products for chewing and dental hygiene
  - Chewable medications such as heartworm preventatives and NSAIDs
  - Dietary supplements
  - Food used to pill the pet

circumstances, all of which should improve the chances for a successful outcome.

One should first determine who lives in the household with the patient, including whether there are other pets, particularly those to whose food the patient might have access. Ask whether one or multiple persons regularly feed the patient. Inquire about the feeding methods. Is the patient offered food free choice or is it fed at specified meal times? Is the feeding portion measured, and what type of device is used to measure the food? Never assume that the proverbial "cup" of food means an 8-fl oz (236.6 ml) measuring cup. Inquire about the patient's feeding behavior. Is this individual a greedy eater or does it prefer to graze on its food throughout the day? Does the patient beg for food between meals? Does the patient share feeding bowls with other pets? Is this pet allowed unsupervised time outdoors when it may hunt or scavenge food?

Obtain the precise names of any commercial pet foods and treats that the patient receives and the specific amounts fed. Often the caregiver will not be able to provide this information accurately by recall alone and will need to check labels and measure feeding portions. Specify that dry pet foods be measured with a standard 8-fl oz measuring cup or if possible, with a gram scale.

When inquiring about treats, specifically ask about products that are used to promote chewing and dental hygiene. People do not always consider such things treats, and many of the products used for this purpose are high in calories. Ask about the kinds and amounts of table foods or scraps that are given to the patient, and if a home-prepared diet is being used, request a detailed recipe. Inquire as to whether the pet routinely receives any supplements or medications that are disguised with food. Some supplements (e.g., fatty acids) can contain a significant number of calories. In addition foods that are typically used to pill a dog or cat, such as cheese, lunch meats, or peanut butter, can be high in fat and calories.

The caregiver may have to go home and keep a food diary for a few days before they can accurately answer all of these questions, and it may, in fact, be impossible to quantify the pet's energy intake from the information obtained, especially when a pet is receiving significant amounts of table foods and treats. However, discovering that such feeding practices exist in a household in advance will reveal the issues that must be addressed in order to implement a successful weight loss program.

FORMULATION OF THE WEIGHT LOSS PLAN

Ideally, the diet history will have provided an accurate accounting of the patient's daily caloric intake. If this is the case and the patient is currently eating a properly balanced diet, weight reduction may be achieved simply by restricting the current calorie intake by 20–40%. Unfortunately, an accurate diet history is not always obtainable and in that circumstance, the first step in formulating a weight loss plan is to decide upon the patient's weight loss goal (Box 9.2).

This should not necessarily be based upon the pet's ideal body weight. It should depend more on just how overweight the pet is. It can be more important to set a reasonable goal and accomplish it than to set an overly ambitious goal and have the pet's caregiver become discouraged and abandon the program. It may be necessary to repeat a program several times for an individual animal in order to reduce it to an optimal body weight.

The second step is to estimate the patient's maintenance energy requirement (i.e., the caloric intake necessary to maintain the patient at its current weight). As previously mentioned, ideally this information would be obtained from the dietary history. However, it is often impossible to quantify an individual pet's caloric intake accurately because feeding portions are not measured, because it is fed with other pets, or because the types and amounts of foods offered the pet vary from day to day. In such cir-

BOX 9.2. FORMULATING A WEIGHT LOSS PROGRAM.

- Perform a physical examination including a BCS and any indicated diagnostic work-up such as a biochemistry panel.
- Obtain a thorough diet history.
- Weigh the patient on an accurate scale and set the weight loss goal.
- Estimate the patient's optimal body weight.
- Estimate the patient's current MER from the diet history or its optimal body weight and activity level.
- Set the level of caloric restriction.
- Choose the diet and calculate the food dosage.
- Tailor a program to meet the needs and preferences of the patient and its caregiver. Include recommendations for feeding management, increasing physical activity, and behavior modification.
- Recheck the patient at two- to four-week intervals for weigh-ins on the same scale and to solicit feedback from the caregiver. Adjust feeding management to target weight loss at 1% to 2% of body weight/week and address any problems or caregiver concerns.

cumstances, the patient's maintenance energy requirement must be estimated (see Chapter 3).

The patient's resting energy requirement (RER) should be calculated using an estimate of its optimal body weight ($RER = Wt_{kg}^{0.75}$). This is because the RER reflects the energy needs of metabolically active tissues such as the cardiac muscle and the central nervous system. Adipose tissue does not contribute greatly, relatively speaking, to the RER, but does account for almost all of the excess body mass in overweight individuals. The maintenance energy requirement is then estimated by applying an activity coefficient to the calculated resting energy requirement. The typically recommended activity factor for adult maintenance is 1.6; however, overweight and obese pets are often sedentary, and their activity level may be more accurately represented by a lower coefficient.

The third step is to calculate how many calories the pet should receive each day to achieve adequate caloric restriction for weight loss. Typically the recommendation is to restrict the pet to 60–70% of the calories it would normally require to maintain its current weight. The final step is to calculate a food dosage for the patient based on the pet foods that it will be receiving, so that the caregivers have clear and specific feeding directions.

Dietary Considerations

Both commercial and therapeutic diets formulated for weight loss are available. In general, these foods have a reduced caloric density that is achieved by lowering the fat content and/or increasing the fiber content. A major advantage of using these foods over conventional maintenance diets is that most have been formulated to contain increased amounts of protein, vitamins, and minerals in order to compensate for caloric restriction and possible decreased bioavailability of these nutrients when fiber content is increased. Furthermore, increasing dietary protein has been shown to help preserve lean body mass during weight loss in both dogs and cats (Hannah and Laflamme 1998; Laflamme and Hannah 2005).

Along with decreasing caloric density, the addition of fiber to a pet food may enhance satiety. In two separate investigations, dogs decreased voluntary food intake when offered free-choice access to dry foods supplemented with fiber compared to their intake while eating a lower fiber diet (Jewell and Toll 1996; Jackson et al. 1997). A third study, where dogs were fed canned diets, did not find any satiety effect from fiber supplementation (Butterwick and Markwell 1997). This investigation differed from the other two studies in that the subjects were overweight dogs whose food intake was limited to promote weight loss. It may be that the satiety effects of fiber are overridden when food intake is restricted.

Feeding canned foods, which are high in moisture content, or adding water to a pet's food is another means of reducing caloric density. Food intake in cats, in particular, appears to be mediated by volume (Stoll and Laflamme 1995). Switching from dry to canned cat food could improve satiety in addition to enhancing portion control.

There has been speculation that lower carbohydrate diets may be more suitable for promoting optimal body weight in cats (Zoran 2002). This is based on the carnivorous metabolism of the cat, which makes it less efficient at digesting and metabolizing carbohydrates than omnivorous species. To date there has been only preliminary investigation of the use of lower carbohydrate cat foods for weight loss or maintenance. Most canned cat foods are lower carbohydrate and could be used for the purpose of maintenance (however, canned maintenance pet foods in general will likely be too limiting in essential nutrients to be safely used for the caloric restriction necessary for active weight loss). Most dry cat foods, however, contain substantial carbohydrate content, and the few that do not are high in fat and consequently high in calories. One investigation found that total caloric intake, but not carbohydrate content, of the diet fed determined weight loss or

gain in group-housed cats (Michel et al. 2005). Substituting dietary fat for carbohydrate does not appear to support dietary carbohydrate as the cause of obesity in cats. A recent investigation reported no significant effect on body weight in young, mature sexually intact cats, free fed purified diets with a similar protein–energy ratio and a carbohydrate content between 24% and 64% ME. High dietary fat induced overconsumption and weight gain in the cats when feed at 64%, but not less than 44% ME (Backus et al. 2007).

Many other nutrients or dietary supplements have been proposed for weight loss effects in dogs and cats, although most have not been critically evaluated. Table 9.3 lists a number of these compounds that are available as supplements, some of which also have been incorporated into commercial and therapeutic pet foods.

Table 9.3. Nutrients and Dietary Supplements That Have Been Proposed as Aids for Weight Reduction

Compound	Investigations in Companion Animals	Comments
L-carnitine A metabolite involved in mitochondrial transport of long-chain fatty acids	Dogs and cats	May increase the rate of weight loss while promoting retention of lean body mass in companion animals during caloric restriction. Effects are modest and inconsistent (Sunvold et al. 1999; Center et al. 2000; Gross et al. 2000).
CLA (conjugated linoleic acid) Isomers of the omega-6 fatty acid linoleic acid	Dogs and cats	Effects on weight loss in human studies are inconsistent. No effects reported on body weight and body composition in one study of normal cats and two studies of dogs on weight loss regimens (Leray et al. 2006; Bierer et al. 2006; Jewell et al. 2006).
Chromium An essential trace element	Dogs only	Purported to enhance weight loss and reduction in body fat when used in conjunction with caloric restriction but no companion animal study to date has shown any benefit from supplementation (Gross et al. 2000).
DHEA (dehydroepiandrosterone) A metabolite involved in steroidogenesis	Dogs only	Supplementation has enhanced weight loss in dogs during caloric restriction; however, there are undesirable side effects from increased sex-hormone production (MacEwen et al. 1991; Kurzman et al. 1998).
Pyruvate A nonessential metabolite of carbohydrate metabolism	Dogs only	Supraphysiological supplementation in humans may enhance weight loss and reduction in body fat; however, a single study involving dogs on a weight loss regimen reported no effect of supplementation (Zhang et al. 2004).
Omega-3 fatty acids Essential and nonessential polyunsaturated fatty acids	Dogs only	May increase energy expenditure through the upregulation of mitochondrial uncoupling protein. Supplementation enhanced weight loss in one preliminary study of dogs during caloric restriction (Ishioka et al. 2004).
DAG oil (diacylglycerol oil) A non-essential fat	None	Human studies suggest that substitution of DAG oil for other fats in food may enhance weight loss and reduction in body fat; however, there are no studies in companion animals to date.
Amylase inhibitors Enzyme inhibitors of plant origin	None	Impair carbohydrate digestion; however, no clinical efficacy has been demonstrated in human weight loss trials, and the one report in dogs that exists suffers from study design concerns.

Exercise

While caloric restriction is the cornerstone of a weight reduction plan for a dog or cat, increasing energy expenditure is another way to achieve a negative energy balance. This is easier said than done, however, as it will generally require a greater commitment on the part of the caregiver, and may be contraindicated due to preexisting health conditions in some individuals.

What is known about the duration and intensity of activity necessary to promote weight loss comes from the human literature, as there have been no investigations that have objectively assessed the range of activity typical of pet dogs and cats or the contribution of increased exercise to successful weight loss in overweight companion animals. These are areas that deserve investigation. However, caregivers can be coached on ways to increase their pet's activity level even in the absence of data on which to base clear cut recommendations. Anecdotally, physical therapy techniques, such as exercise on an underwater treadmill, have been useful adjuncts in weight loss programs for dogs.

Tailoring the Program to the Patient

While the basic design of a weight loss program is to induce a negative energy balance by restricting caloric intake through dietary modification and increasing caloric expenditure through the promotion of physical activity, there are many ways to go about achieving this goal. To be successful, the program should be tailored as much as possible to fit the lifestyle of the patient's household. Caregivers are unlikely to embrace proposed radical changes in behavior such as a ban on treats or an ambitious exercise program. Obtaining a thorough dietary history will reveal the needs and the preferences of both the caregiver and patient. Table 9.4 lists some considerations to address when designing a weight loss program.

Table 9.4. Considerations for the Design of a Weight Loss Program

- Multi-pet Households
  - Can the pets be fed separately?
  - To what lengths is the caregiver willing to go to feed the pets separately?
- Feeding Methods
  - Can the patient be fed portion-restricted meals?
  - Can the caregiver's lifestyle accommodate meal feeding?
- Diet
  - Will the patient tolerate a change in diet?
  - Is the caregiver willing to change the patient's diet?
  - Will the patient tolerate reduced portions?
  - Is the caregiver willing to reduce feeding portions?
- Treats
  - If the patient receives excessive amounts of food as treats will the caregiver accept modifications of the kinds and amounts of treats offered?
- Exercise
  - How active is the patient and can it tolerate an increase in activity level?
  - Can the caregiver's lifestyle accommodate measures for increasing the patient's activity level?
- Household
  - Will all the people in the household cooperate with the program?

ASSESSMENT OF THE WEIGHT LOSS PLAN

The success of a weight loss program hinges on follow-up. Throughout the entire program the patient should be monitored on a regular basis (every 2 to 4 weeks) in order to assess whether it is losing weight at an appropriate rate and whether the caregiver has any concerns so that the plan can be modified as necessary. Maintaining contact throughout the program is the only way to ensure that the patient achieves its targeted weight loss goal.

The pet should be weighed on the same scale during each visit to evaluate its progress. It is not uncommon to have to make adjustments to the feeding recommendations if the pet is not losing weight as quickly as anticipated and if there is no indication that the caregiver is not adhering to the program, or, alternatively, if the pet is losing weight at too rapid a rate. The calculation of the maintenance energy requirement of an overweight patient involves some guesswork, and so the need to fine-tune the plan should be expected. The rate of weight loss should be targeted at 1–2% of body weight per week (see Box 9.3). One

BOX 9.3. ESTIMATING TIME NEEDED TO ACHIEVE WEIGHT LOSS GOAL

The time it will take to achieve the weight loss goal can be estimated by multiplying the kilograms of weight the pet needs to lose by 7,700 kcal/kg. Dividing the resulting number by the daily caloric deficit provides an estimate of how long it will take to lose the weight (e.g., a cat that needs to lose 1 kg and is being restricted by 100 kcal/day below its maintenance energy requirement will need to be on the diet approximately 77 days or 11 weeks). Alternatively, one can use the rate of weight loss and BCS to estimate how long the plan will take. A BCS indicating the pet is 15% overweight coupled with a weight loss rate of 1% will mean the pet will take 15 weeks to lose the needed weight.

investigation that examined weight loss in dogs on different degrees of caloric restriction found, as one would expect, that those dogs that were the most calorically restricted lost weight the most rapidly (Laflamme and Kuhlman 1995). However, these same dogs were the ones most predisposed to regain the weight when they came off of the diet.

The follow-up visit is also the time to inquire whether anyone in the household has been experiencing difficulties in implementing the weight reduction plan. Often unforeseen issues can arise. The patient may not accept the recommended changes in diet or feeding management and may begin to exhibit unacceptable behaviors such as stealing food or breaking into the trash. The human members of the household may have difficulties adhering to the program because of the pet's behavior, their own time constraints, or feelings of guilt over withholding food or treats from their companion. Undetected problems that go unresolved can result in the caregivers becoming discouraged with the program and giving up.

Safety and Efficacy of Weight Loss Programs for Companion Animals

There have been published studies evaluating the efficacy of weight loss programs for dogs and cats. A number of these studies, some conducted in a controlled setting such as a kennel and some conducted as clinical trials, have reported excellent results (Laflamme and Kuhlman 1995; Watson et al. 1995, Center et al. 2000; Impellizeri et al. 2000; Burkholder et al. 2001). However, success in a clinical setting can be challenging. One investigation that evaluated a weight loss program in pet dogs experienced a significant dropout rate (28 of 60 dogs) over the course of the study (Yaissle et al. 2004). However, the dogs that did complete the 6-month weight reduction program lost, on average, approximately 15% of their initial body weight.

The same investigations of efficacy of weight reduction programs for companion animals have found them to be safe. The greatest concern over the safety of aggressive food restriction for cats is the risk of inducing hepatic lipidosis. Investigations where overweight cats were restricted from 25 to 60% of normal maintenance energy requirement found that the cats lost weight while maintaining their appetite without any changes in serum chemistry (Armstrong et al. 1992; Watson et al. 1995). These findings suggest that the risks of inducing feline idiopathic hepatic lipidosis by a weight reduction regimen in an otherwise healthy cat are minimal. However, caregivers of cats who undertake a weight loss plan should be familiar with the signs of hepatic lipidosis and should be instructed to seek medical attention for their cat if it becomes anorexic.

ADJUSTMENT OF THE WEIGHT LOSS PLAN

When a patient is not losing weight at the anticipated rate, the first step is to review the feeding plan with the caregiver to determine whether all aspects of the plan are being adhered to and whether any problems have arisen. If the caregiver adhered to the plan, then in most cases it will be necessary to adjust the amount of kilocalories fed up or down as necessary (a 10% adjustment would be a reasonable place to start) to achieve the targeted rate of weight loss. Many patients who successfully lose weight will reach a plateau in their rate of weight loss after a period of time. This is the likely consequence of a reduction in metabolic rate due to several factors including metabolic adaptations and the inevitable loss of some lean body mass.

Even when care has been taken to tailor a weight reduction plan to an individual household, problems can arise. There are a variety of tactics that can be used to motivate the caregiver toward success (Table 9.5).

One common concern that is voiced is that the patient behaves as if it is very hungry and may be engaging in undesirable behaviors such as stealing food. There are a number of ways this situation can be addressed. If the patient is not already consuming a reduced calorie pet food, this should be suggested. Switching to a food with a lower caloric density will permit feeding larger portions. Feeding canned rather than dry food may be more satisfying for some pets. As previously mentioned, there is evidence that cats do not readily compensate for the reduced caloric density of canned foods, and studies have shown that adding water to foods to decrease caloric density (e.g., eating soup rather than a casserole) has a satiating effect for human subjects (Rolls et al. 1999). Another tactic is to add low calorie nonstarchy vegetables such as carrots or green beans to the meal.

Feeding the pet three or four small meals a day rather than one or two large ones can be helpful in several ways. Having part of the daily food ration available to feed throughout the day should help decrease the temptation to "cheat" by giving treats when the pet begs for food. For cats this approach will help to mimic the more natural feeding pattern of the species. Also, more calories are expended in digesting and assimilating nutrients from multiple small meals than from one or two large ones (Leblanc and Diamond 1986).

The diet history will reveal the households where feeding the pet is a bonding activity. Giving the people in the household a prescribed treat allowance can help in

Table 9.5. Weight Loss Program Troubleshooting Tips

- Food-seeking behavior
  - Use a therapeutic reduced calorie diet
  - Switch to canned food or add water to the food
  - Add nonstarchy vegetables to the meal
  - Feed the daily food portion in multiple small meals (including one shortly before bedtime)
  - Substitute other forms of attention (e.g., grooming, play) for treats
  - Give the caregiver a daily treat allowance
  - Keep pets out of the kitchen during food preparation or the dining areas during meals
  - Serve the meal in a food puzzle
  - Environmental enrichment
- Multi-pet households
  - Meal feed in separate rooms
  - Feed on a raised surface (cats)
  - Construct or purchase a creep feeder (cats or small dogs)
- Sedentary pets
  - Feeding puzzles
  - Food-motivated play
  - Environmental enrichment
  - Start a walking program or hire a dog walker (dogs)
  - Physical therapy

these cases. Most people are familiar with counting calories, so a treat allowance will give the household some flexibility in how they give treats from day to day. Set the allowance at 10% of the pet's daily caloric intake and provide the caregivers with information about the caloric content of the pet treats they use, or with some low-calorie alternatives. The calorie content of commercial pet treats can usually be obtained from the label or the manufacturer through a toll-free number or website.

Because food is commonly used for bonding with a pet, there is often a behavioral component to begging in addition to hunger. Ignoring these behavioral aspects of feeding will doom a program to failure. The caregiver can be counseled to substitute play or grooming, in addition to lower calorie treats, as alternatives to feeding calorically dense foods and treats for bonding. Another tip to help curtail begging behavior is to keep the pet out of the kitchen during food preparation or dining areas during meals.

Using food puzzles or some other type of ploy to make a pet work for its food may also help to decrease begging. This approach and other forms of environmental enrichment may have an added benefit of increasing the pet's energy expenditure (Clarke et al. 2005).

Multi-pet households present their own challenges, as it can be difficult to restrict portions for the pet on the weight reduction diet when food for other pets is available. Ideally all the pets in the household would be meal fed and fed separately. It can be difficult to transition pets that had been previously fed free choice to meal feeding, as well as to make certain that the dieting pet does not have access to the other pets' food. Sometimes feeding the pets in separate rooms will be the solution. With cats, feeding on a counter or other raised surfaces will keep food away from a dog or an overweight cat that is not able to jump or climb. It is also possible to construct or purchase feeders that have openings that will permit a thin pet access to the food but exclude the overweight one.

One final challenge is increasing activity level for sedentary pets. As already mentioned, this will generally require a greater commitment from the caregiver than changes in feeding management. Some things that can be tried are using feeding puzzles or moving food bowls throughout the house. Food can be used to motivate the pet to climb, jump, and run, especially if the pet's environment is enriched with objects to facilitate these activities. The services of a pet walker can be used if the caregiver is unable to exercise the pet himself. And if the caregiver has access to a veterinary physical therapy facility, regular use of a swimming pool or underwater treadmill can be incorporated into the program. This approach should be of particular benefit for dogs with orthopedic disease.

SUMMARY

Many companion animals are overweight or obese and, as a consequence, are at risk of impaired health and reduced longevity. To address this problem, people must learn how to body condition score their pets and be able to recognize when a pet is not in optimal condition. When veterinarians perceive that a pet is overweight, they must bring it to the attention of that pet's caregiver. A successful weight reduction program begins with a thoroughly conducted diet history and should be tailored to the individual household to increase the likelihood of adherence. Follow-up rechecks are absolutely essential for monitoring the patient's progress and adjusting the plan as necessary, thereby ensuring the success of the program.

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Nutritional Management of Orthopedic Diseases

10

Herman Hazewinkel

INTRODUCTION

The percentage of patients with orthopedic (i.e., nontraumatic) disease has been reported to be around 10%, although this figure varies depending upon the type of veterinary clinic and its location. The percentage of some orthopedic diseases is higher in large dogs (Lafond et al. 2002), with particular breeds more at risk. The popularity of these at-risk large breed dogs can differ considerably between countries; e.g., Bernese Mountain dogs are in the top 10 among popular breeds in some countries, whereas in other states they rank much lower. Historically, orthopedic diseases are less well recognized in cats than in dogs, but this is changing as specialization in feline medicine increases.

Nutrition plays a role in skeletal growth and development, may have an influence on the occurrence of skeletal diseases, and can be applied to support treatment of orthopedic patients. This chapter will discuss the relevant nutritional aspects in all three roles after a short overview to facilitate the understanding of the particular role of nutrition.

Bone Composition and Calciotropic Hormones

Skeletal growth can be divided into three interrelated processes: (1) endochondral ossification, which includes growth, maturation, and apoptosis of chondrocytes followed by bony replacement of cartilage; (2) periosteal growth, including lamellar new bone formation; and (3) remodeling, including the removal of newly formed metaphyseal bone to adapt the shape of the bone, the removal of bone at the endosteal site of long bones and in tunnel-like structures around growing soft tissues, and the remodeling of lamellar bone into Haversian structures. Endochondral ossification takes place in primary and secondary ossification centers around birth and in growth plates between the epiphyses and metaphyses, as well as in the cartilage layer covering the epiphyses during the growth phase. Cancellous bone remains in the metaphyses and diaphyses of long bones as well as in vertebral bodies and is easily accessible by bone-removing cells. Periosteal growth takes place in the diaphyseal area of the long bones and in flat bones like the pelvis, ribs, and skull. Remodeling is especially seen at the endosteum and the metaphyseal areas and in vertebral and nutritional canals. The cell types involved in bone growth and remodeling are chondrocytes forming the cartilage matrix, chondroclasts removing that matrix after its mineralization, and osteoblasts forming osteoid on the cartilage template (in case of endochondral ossification in ossification centers and metaphyses) or directly on the periosteum to stimulate its mineralization by alkaline phosphatase secretion. Osteoclasts are able to resorb mineralized osteoid with the aid of acid phosphatase, and osteocytes are able to communicate with peripheral osteoblasts via their canalicular system and resorb bone locally. The skeleton provides a solid framework for muscles and a harness for delicate structures but is also a depot for minerals (Table 10.1), of which calcium is the most biologically important element, playing a vital role in blood clotting, muscle contraction, and enzymatic processes. More than 98% of the body's

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Table 10.1. Content and Ratio of Calcium, Phosphorus, and Magnesium in Dogs

	Calcium	Phosphorus	Magnesium
% of adult body weight	1–1.5%	0.5–0.8%	~0.25%
% present in skeleton	98%	80%	50%
Absorption	Active (vitamin D regulated) and passive diffusion	Active (vitamin D regulated) and passive diffusion	Facilitated and passive diffusion
Octocalciumphosphate $Ca_8(HPO_4)_2(PO_4)_4{\cdot}5H_2O$	8 :	6	N/A
Whitlockite $Ca_9Mg(HPO_4)(PO_4)_6$	9 :	7 :	1
Na-containing apatite $Ca_{8.5}Na_{1.5}(PO_4)_{4.5}(CO_3)_{2.5}$	17:	9	N/A
Carbonated apatite $Ca_9(PO_4)_{4.5}\ (CO_3)(OH)_{1.5}$	18:	9	N/A
Hydroxyapatite $C_{10}(PO_4)_6(OH)_2$	10:	6	N/A

calcium is stored in the skeleton as stable crystals (including hydroxyl apatite) and in labile calcium compounds (including calcium phosphate and calcium bound to plasma albumin), which can quickly be mobilized. Of the remaining 1%, half of it is in the extracellular fluid as the biologically active, ionized form. Of the body's phosphorus, 80% is stored in the skeleton and is of major importance in the formation of calcium salts and thus mineralization of newly formed cartilage and osteoid.

Chemical Composition of Bone

After musculature (40–57% of body weight), the skeleton makes up the largest part of the body weight of an adult dog, (8–13%), whereas it is 10% in newly born puppies (Meyer and Zentek 2005). The composition of an adult dog by weight includes 1–1.5% calcium, 0.5–0.8% phosphorus, and 0.25% magnesium of which 98%, 80%, and 50%, respectively, is present as mineral in the skeleton (Meyer and Zentek 2005). Whole bone, including marrow and periosteum, consists of 33% organic components (including 95% collagen, 5% glycoproteins, and sulphated glycosaminoglycans), 17% water, and 48% inorganic material primarily calcium, phosphate, carbohydrate, and magnesium (Kincaid and Van Sickle 1983; Jee et al. 1970). The various skeletal locations reveal marked differences in composition; lumbar vertebrae can contain twice the amount of water, depending on the amount of cancellous bone. Trabecular bone has more water and less ash than cortical, and it has slightly less organic material, although this also can differ considerably: The ash percentage in vertebrae is 50% and in mandibles only 7% of the bone weight.

Minerals in bone are formed in different phases, starting with octocalciumphosphate and whitlockite, followed by sodium-containing apatite, carbonated apatite, and eventually hydroxyapatite in the adult skeleton. Mineral complexes other than apatite are of interest for ionic exchange. The grams of calcium per cm^3 of bone increases with advancing age; in Beagles from 0.468 and 0.536 g at 6 weeks to 0.512 and 0.612 g at 11 years of age, in low-and-high density areas, respectively. Not only age, but also mineral composition of the diet may influence the mineral composition of bone. (Hazewinkel and Schoenmakers 1995; Jee et al. 1970).

Mineral Composition During Growth

Joint cartilage has a high heterogeneity of chondrocyte types and arrangements within the matrix, with its collagen fibers encored in the calcified zone with hydroxyapatite salts (Table 10.2) (Poole et al. 2001).

In one study, seven growing Miniature Poodles were raised on the same food formulated according to the 1985 National Research Council (NRC) guidelines. Partial weaning was started at 3 weeks of age and completed by 6 weeks of age.

Magnesium content was higher in rib biopsies at 11 weeks than at 21 weeks of age in these Miniature Poodles (Table 10.3) (Huis in 't Veld et al. 2001). When maturation proceeds, firmer calcium-phosphate crystals are formed, reducing the magnesium content. It is also possible that

whitlockite is exchanged for other apatites during growth (Driessen 1980). The increase in the calcium-to-phosphorus ratio, as reported in ruminants (Chicco et al. 1973) was also seen in the dogs of this study.

Comparison with an identical study in Great Danes, raised on the same food and investigated according to the same procedure, revealed that the calcium-to-phosphorus ratio did not increase in this time period (1.570 vs. 1.527 at 11 and 21 weeks, respectively). This finding was probably due to the slower skeletal maturation in giant breed dogs when compared to small breed dogs. There was also a decrease in whitlockite content (0.302 mmol/cm^3 at 11 weeks vs. 0.238 mmol/cm^3 at 21 weeks of age) (Huis in 't Veld et al. 2001). Excessive calcium intake will increase the calcium content and decrease the magnesium content in the bones of young dogs (Hazewinkel and Schoenmakers 1995). However, when excess vitamin D was given to Great Dane dogs starting at partial weaning (i.e., 10 or 100 times the recommended dietary content), the ratio of calcium to phosphorus increased, but the amount of whitlockite decreased at the same rate as in the controls (Huis in 't Veld et al. 2001; Hazewinkel and Tryfonidou 2002).

In addition to age and food composition, skeletal location influences bone composition. In low density areas, 1.02–1.28 g of hydroxyapatite was found per cm^3 of bone in adult Beagles. In the high density bone areas, this was 1.23–1.54 g hydroxyapatite, without any effect on breaking stress in healthy dogs (Jee at al. 1970).

These analyses illustrate the role of the skeleton as a buffer for excess minerals, as well as an organ with biomechanical functions and its related architecture and composition.

Table 10.2. Biochemical Composition of Cartilage

	Chemical content of cartilage in the extracellular matrix
Water	66–79%
Collagen	60% (% of dry weight)
Mainly collagen II	
Also coll. XI, III, V, VI, X, XII, XIV	
Proteins	8–15%
Glycosaminoglycan	14–23%
Hyaluronate	<1%
Lipid	<1%
Inorganic (ash)	2%

Hormonal Regulation of Calcium

A constant extracellular concentration of ionized calcium is of importance to maintain a variety of physiological processes, which can be life threatening when they do not occur properly due to a deficiency or excess of this element. The uncontrolled input of calcium (i.e., passive diffusion of calcium through the intestinal wall) takes place only in the immature dog and especially in cases of a positive gradient (Tryfonidou, van den Broek et al. 2002). The uncontrolled excretion of calcium via the glomerulae could be as high as 60% of the circulating calcium, being the ultrafilterable amount. Calcium deposition in the skeleton (i.e., in newly formed cartilage and osteoid) is largely a physicochemical process and will take place especially in growing individuals. These uncontrolled processes do not guarantee a constant and sufficiently high enough extracellular calcium level. Hormonal regulation is necessary to accomplish this, adapted to different life stages and environmental influences. There are mainly three hormones involved in the homeostasis of calcium.

During evolution of terrestrial mammals living in a calcium-deprived environment, parathyroid hormone (PTH) became the most important of these calciotropic hormones. Its role is to increase plasma calcium concentration when it decreases. PTH executes this role by increasing reabsorption of calcium from the pre-urine and by activating osteoclasts to resorb bone (i.e., freeing calcium and phosphorus from bone minerals). Under the influence of PTH, the renal threshold for phosphorus will be lowered, with a subsequent increase in phosphaturia. In addition, PTH stimulates the synthesis of another calciotropic hormone, calcitriol.

The product of cholecalciferol (vitamin D) hydroxylation in the liver is 25-hydroxycholecalciferol (25OHvitD),

Table 10.3. Mineral Composition of Rib Biopsies at 11 and 21 Weeks of Age in Miniature Poodles

	Ca (mg ± sd/cm^3)	P (mg ± sd/cm^3)	Mg (mg ± sd/cm^3)	Ca/P ratio	Whitlockite (mmol/cm^3)
11 weeks	377 ± 74	183 ± 35	7 ± 0.42	1.658	0.304
21 weeks	368 ± 11	177 ± 5	6.5 ± 0.3	1.697	0.272

Table 10.4. Similar Plasma Mineral Levels With Significant Differences in Vitamin D Metabolites in Different Breeds

	Ca mmol/L	P mmol/L	PTH (ng/L)	25(OH)vitD nmol/L	$24,25(OH)_2$vitD nmol/L	$1,25(OH)_2$vitD pmol/L
G. Dane	2.8 ± .1	2.7 ± 0.1	62 ± 6.5	14.7 ± 2.8	39.9 ± 3.2	250 ± 9
M. Poodle	2.8 ± .2	2.6 ± 0.1	70 ± 5.0	50 ± 2.0	140 ± 6.0	190 ± 10

Mean (±SEM) of plasma concentrations in nine Great Danes and eight Miniature Poodles, 3 months of age, raised on a diet with 0.94 g Ca and 0.75 g P and 1.14 mcg vitamin D per 100 g dry matter at two times maintenance (Tryfonidou et al. 2003).

and it is the most abundant metabolite of vitamin D in plasma. PTH stimulates the synthesis of an enzyme present in the kidney, 1α-hydroxylase, which is responsible for the hydroxylation of 25OHvitD into calcitriol [$1,25(OH)_2$vitD]. In addition, other hormones and minerals influence vitamin D metabolism causing significant differences in vitamin D metabolism under different circumstances, and even in dogs of different breeds raised under the same circumstances (Hazewinkel and Tryfonidou 2002) (Table 10.4). In Miniature Poodles receiving supraphysiological doses of growth hormone (0.5IU GH per kg body weight per day), the plasma insulin-like growth factor (IGF-1) levels and the 1,25(OH)2vitD production both increased, whereas 24,25(OH)2vitD decreased. As a result the plasma concentrations of the vitamin D metabolites resembled those of Great Danes (Tryfonidou and Hazewinkel 2004). The primary function of calcitriol is to mineralize cartilage and newly formed osteoid. Calcitriol performs this role by increasing reabsorption of calcium from the pre-urine, by acting as a permissive factor for PTH (thus stimulating osteoclast activity), and by increasing the process of active absorption of calcium and phosphorus from the food in the intestine. This hormonally regulated, active absorption is of special importance in growing dogs due to their high calcium requirement combined with low dietary calcium content (Hazewinkel and Tryfonidou 2002).

When the calcium concentration of the intestinal contents is high, calcium will diffuse between the intestinal cells by nonsaturable, paracellular passive diffusion. In addition to calcitriol, another vitamin D metabolite is formed: $24,25(OH)_2$vitD, which has long been seen as a waste product of 25OHvitD in order to avoid providing too much of the biologically active $1,25(OH)_2$vitD. However, recently an important role for $24,25(OH)_2$vitD was demonstrated in endochondral ossification: $24,25(OH)_2$vitD stimulates maturation of chondrocytes and increases the responsiveness of these chondrocytes to $1,25(OH)_2$vitD for further differentiation and matrix mineralization (Wu et al. 2006). In addition, $24,25(OH)_2$vitD increases the bone mineral content (Mortensen et al. 1993) together with reducing osteoclast activity, i.e., reduced bone turnover, contrary to $1,25(OH)_2$vitD (Norman et al 2002).

Calcitonin (CT) is the third calciotropic hormone, which is of special biological importance in animals living in a calcium-rich environment, e.g., saltwater fish. In mammals, the release of CT, which is mainly formed in the thyroid glands, can be caused by an acute rise in plasma calcium concentration as well as in gastrin concentration. A correcting decrease of plasma calcium concentration in mammals occurs mainly via the reduction of osteoclast activity; the ruffle borders of the osteoclasts are retracted instantly under the influence of CT. CT has many more functions and effects, including activation of the satiety center (Tryfonidou, Hazewinkel, and Kooistra 2010).

Growth hormone (GH) is not a calciotropic hormone per se, but one of the major hormones responsible for longitudinal and periosteal growth of the skeleton. GH stimulates the formation of IGF-I in the liver and in target cells including osteoblasts. GH stimulates intestinal calcium absorption by hypertrophy of intestinal cells and directly, or via an increase in IGF-I level, by stimulating $1,25(OH)_2$vitD and suppressing $24,25(OH)_2$vitD production, respectively. IGF-I synthesis can also be stimulated by PTH and by the ingestion of nutritional factors such as protein and energy. IGF-I stimulates bone and collagen synthesis, as well as chondrocyte cell proliferation (and thus longitudinal growth), and to a lesser extent chondrocyte differentiation, and it can suppress GH synthesis and release from the pituitary gland (Tryfonidou and Hazewinkel 2004).

In addition to calcium and phosphorus, other minerals also play a role in bone formation. Magnesium (Mg) is an

important stabilizer of DNA, RNA, and ribosomes, and it is a cofactor in many enzymes and influences bone mineral formation. It is regulated by PTH and vitamin D, and not, importantly, by CT. Mg absorption is not active but facilitated by vitamin D and takes place by diffusion. Mg absorption increases with increasing dietary vitamin D and decreases in cases of excess dietary calcium, phosphorus, or long-chain triglycerides. PTH decreases renal losses of Mg. In addition, Mg excess will be reflected in the plasma and lead to increased Mg content in the bone. Mg stimulates 1 alpha hydroxylation of 25OHvitD and will increase bone turnover. Mg deficiency also causes muscular weakness, but not clinical abnormalities of the skeleton.

THE ROLE OF NUTRITION DURING SKELETAL GROWTH AND DEVELOPMENT

Energy

Energy, provided by carbohydrate, protein, and fat, is the driving force behind food intake. Dietary carbohydrates have not been recognized to be essential for growth in dogs (Meyer 1983), and there are no reports on the relationship between carbohydrate deficiency and skeletal disease. In the case of malnutrition, there is often a deficiency of both protein and energy. Low protein intake will coincide with growth retardation and finally growth cessation and weight loss (Sheffy 1979). Plasma albumin will decrease, especially when protein intake is inadequate in the face of sufficient energy intake (Lunn and Austin 1983; Nap, Mol et al. 1993). Low energy and protein intake will cause a decrease in hepatic IGF-I production and thus a decrease in skeletal growth. Beagles raised from 6 to 25 weeks on a diet with 12% protein [as a percentage of metabolizable energy (ME)] never reached normal body weight, even after being fed a food with 25% (ME) free choice thereafter (Sheffy 1979). Great Danes raised from 7 to 20 weeks of age on a balanced food with 13% (ME) protein, developed hypoalbuminemia and a lower body weight but had no abnormalities in size or skeletal development when compared to controls raised on a diet containing 21% protein (ME) (Hazewinkel and Schoenmakers 1995). Low energy intake is not a common clinical problem (Richardson et al. 2010), and therefore in cases where animals are small for their age, the clinician should also consider a biological variation in body size or growth rate, metabolic diseases such as GH deficiency, hypothyroidism, liver shunt, or skeletal abnormalities like chondrodystrophy (in breeds where it is not part of the breed standard), or rickets.

Excess energy intake is much more common in today's clinical practice. Diets containing an excess of protein (>30 g per 100 g dry weight) will be metabolized, although in some cases one can document an increase in plasma albumin or blood urea nitrogen, reflecting the increased deamination of protein and not a malfunction of the kidneys (Romsos et al. 1976). In a study in growing Great Danes, raised on a diet with 29% protein (ME), except for an increase in plasma albumin and blood urea nitrogen concentrations, no differences were found in plasma total protein, growth rate, calcium metabolism, or skeletal development (Nap, Hazewinkel et al. 1993b).

Excess fat cannot only predispose an animal to excessive calorie consumption, thereby increasing body weight, but can also decrease the intake of essential nutrients when these are not adapted to the high energy content of the food. Dietary fat is very readily absorbed and converted more efficiently into body fat than dietary carbohydrates or proteins without affecting the growth in lean body mass (Romsos et al. 1976). When the fat content of the food was increased from 8% to 24% of dry matter in a diet with 22% protein, 10% ash, and no fiber added, the metabolizable energy increased by 22.5%. This resulted in a higher percentage of body fat and an increase in body weight when fed free choice compared to control dogs raised on an 8% fat (DM) diet (Richardson et al. 2010).

There are a variety of studies demonstrating the deleterious effects of overnutrition on skeletal development (Hedhammar et al. 1974; Lavelle 1989; Alexander et al. 1988), causing osteochondrosis and poor hip conformation and resulting in secondary osteoarthrosis in multiple joints (Kealy, Olsson et al. 1992) (Table 10.5). Since overnutrition often includes providing an excess of all nutrients, it is not obvious if the causative role of excess calories is a matter of overweightedness alone. Since excess minerals (Hazewinkel, Goedegebuure et al. 1985; Schoenmakers et al. 2000) and vitamin D (Tryfonidou, Holl, Vastenburg et al. 2003), but not protein or carbohydrate (Nap and Hazewinkel 1994), disturb skeletal development severely, and excessive fat intake has no influence on calcium metabolism (Hallebeek and Hazewinkel 1998), a deleterious role for specific nutrients is to be expected (see Fig. 10.1). Therefore, the most relevant nutrients in clinical practice will be discussed in the following sections.

Calcium, Phosphorus, and Vitamin D

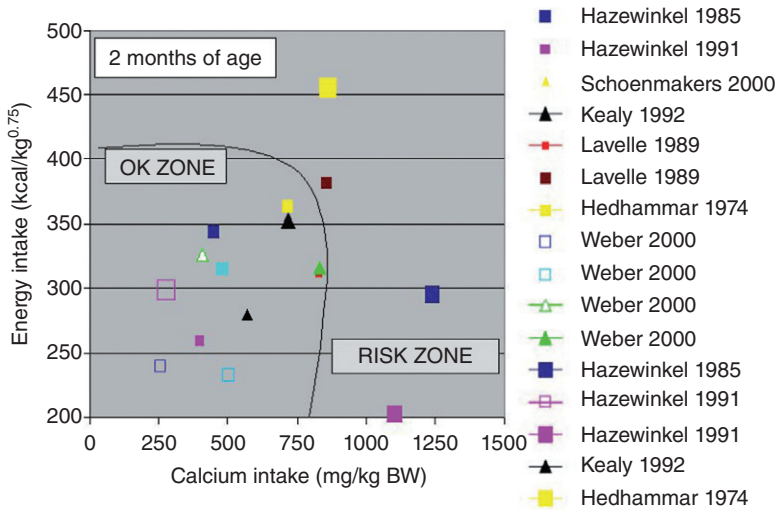
Calcium Deficiency

Calcium is required for biological processes and for skeletal mineralization. The calcium requirement for growing dogs range between 0.33% and 1.2% of calcium on a dry matter basis (Table 10.5) In rapidly growing animals, the daily calcium requirement is much higher than in slower growing animals. In rapidly growing Great Danes, the

Table 10.5. Investigations of the Influence of Excess or Deficiencies on Skeletal Development

	Hedhammar et al. 1974	Lavelle 1989	Hazewinkel et al. 1991	Nap et al. 1991	Nap et al. 1993	Schoenmakers et al. 1999	Tryfonidou et al. 2002
Breed of research dog	Great Dane	Great Dane	Great Dane	Great Dane	Miniature Poodle	Great Dane	Great Dane
Food composition per 100 g (DM)							
ME in kcal (kJ)	501 (2094)	431 (1802)	402 (1680)	359 (1500)	359 (1500)	N/A	450 (1884)
Crude protein	36	29.6	21	21	21	21	27
Crude fat	13.7	14.4	9.9	9.7	9.9	10.2	15
Calcium	2.05	2.3	1.1	1.0	1.0	1.04	0.95
Phosphate	1.44	1.6	0.9	0.9	0.9	0.82	0.75
Vitamin D (in mcg)	N/A	N/A	2.77	2.77	2.77	2.76	1.14
Variables in study	*Ad lib* or restricted to 66%	*Ad lib* or restricted to 60%	Ca 0.55%, 1.1%, or 3.3% (DM)	Proteins: 31, 23, or 14% (DM)	Calcium: 0.05%, 0.33%, 1.1% and 3.3% (DM)	Calcium: 1.1% and 3.3% calcium starting at different ages	Vitamin D content: 1.14; 10.0; 135 mcg/100 g (DM)
Clinical, radiological, and pathological findings	*Ad lib* group had higher rates of osteochondrosis, radius curvus syndrome, poor hip conformation, wobbler syndrome	No differences in skeletal problems between both groups	Pathological fractures in 0.55% Ca group; severe osteochondrosis, radius curvus and wobbler in the 3.3% Ca group	No differences in skeletal problems between groups	Pathological fractures in 0.05% Ca group; no clinical pathology in .33% Ca, 1.1% Ca, or 3.3% Ca group	3.3% Ca from 3–6 weeks only: panosteitis at 4 mo. 3–17 weeks: Hypophosphatemic rickets 6–26 weeks: severe osteochondrosis and radius curvus	1.14 mcg vitamin D per kg food: normal endochondral ossification; at 10 mcg and 135 mcg vitamin D per kg food: slight and severe osteochondrosis

Breed of research dogs and dietary composition with their variables are summarized for different studies together with the clinical and radiological findings in these dogs.



Footnote: The graph depicts the calcium intake (in mg Ca per kg body weight) provided together with the energy intake (expressed as kcal per $kg^{0.75}$) for different studies in large breed dogs (e.g., Labradors, German Shepherds, Newfoundlands, Great Danes) of 2 months of age with special attention to the development of skeletal diseases (including osteochondritis dissecans, retained cartilage cone with radius curvus syndrome, and hip dysplasia). The area left of the curved line represents the calcium intake with no or minimal skeletal abnormalities, whereas right of the curved line is the potentially deleterious zone. The numbers refer to the authors in the reference list (modified from Hazewinkel and Mott 2006, with acknowledgement to Dr. M. Weber).

Fig. 10.1. Potential deleterious effects in skeletal development in large breed puppies raised on controlled calcium and energy intake. Reference to the different studies as included in the reference list (referring to the year of publication).

daily calcium deposition in the skeleton can be as high as 225–900 mg calcium per kg of body weight, whereas in Miniature Poodles the daily deposition of calcium in the skeleton sufficient for undisturbed skeletal mineralization was 140 mg calcium per kg of body weight (Nap, Hazewinkel et al. 1993a).

Dietary calcium deficiency can be caused by feeding meat-based, home-prepared diets with insufficient supplementation of calcium salts, by feeding unbalanced commercially prepared diets, or by feeding poor quality diets with an excess of phytates that bind intestinal calcium as insoluble and nonabsorbable complexes. Chronic calcium deficiency will not cause a decrease in body growth; the mineralization of the skeleton will have a tendency to result in a decrease in plasma calcium levels and will induce hyperparathyroidism. As a result, there will be an increase in bone resorption by activated osteoclasts and osteocytes. In cases of chronic calcium deficiency, calcium resorption from bone and calcium accretion (i.e., skeletal mineralization) are both significantly increased (Nap, Hazewinkel et al. 1993b; Hazewinkel, van den Brom et al. 1991), with a subsequent increase in plasma alkaline phosphatase levels. Thus bone turnover is significantly increased in animals with dietary-induced hyperparathyroidism. This explains the radiological and pathological findings in the skeleton: long bones reveal a normal growth in length, together with an excessively increased osteoclastic bone removal especially in the endosteum (resulting in

a wide intramedullary cavity) and in the areas of cancellous bone. The cortex can become so thin that it cannot withstand normal muscle contracture or the body weight of the animal, leading to pathological fractures (i.e., greenstick and compression fractures) (Fig. 10.2). Compression fractures of vertebrae can cause paralysis and can worsen the prognosis of the animal. The PTH-induced increase in $1,25(OH)_2vitD_3$ plasma levels explains the normal mineralization of the growth plate cartilage, visible as a white area bordering the growth plates of normal width. This finding is important to aid in the differentiation between alimentary secondary hyperparathyroidism or hypovitaminosis D (see the section on rickets).

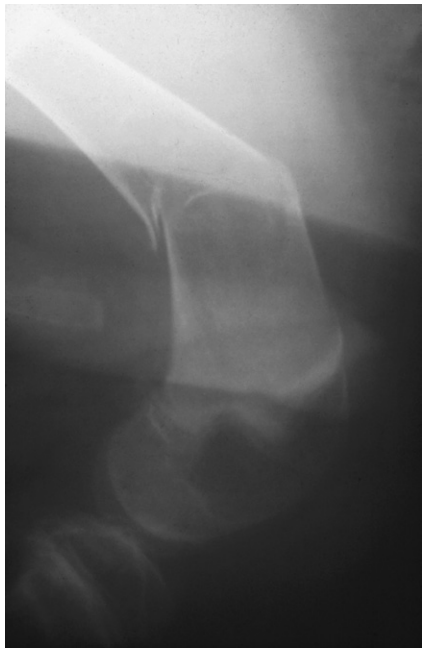


Fig. 10.2. Young dog with hyperparathyroidism due to calcium deficient diet, causing folding fractures in the long bones ("greenstick fractures") due to the narrowing of the cortex. Notice the poor contrast difference between bone and soft tissues, and the growth plate of normal width with adjacent white area of mineralized cartilage.

The diagnosis can be made by taking a diet history, careful radiological interpretation (poor contrast between bone and soft tissues, greenstick and compression fractures, wide medulla, bended flat bones, normal growth plates), and in some cases measurement of plasma PTH concentrations. In most cases, plasma concentration of calcium will be kept in the physiological range (although at the lower end) by the calciotropic hormones with phosphorus plasma levels normal to slightly above normal combined with increased urine levels of phosphorus (Table 10.6). Analysis of plasma calcitriol concentration will reveal elevated levels compared to normal dogs of the same breed and age. Bone biopsies will demonstrate thin cortices and thin cancellous bone spiculae, no unmineralized osteoid, an increased amount of multinucleated osteoclasts within Howships lacunae reflecting their high activity, and growth plates will be normally mineralized and of normal width [Fig. 10.3(a)]. The most practical approach for confirming the diagnosis based on clinical and radiological investigation is to institute treatment and reevaluate the skeletal status after 3 weeks. Differential diagnoses are rickets (see below), osteogenesis imperfecta (a rare hereditary disease with abnormal bone collagen), and renal hyperparathyroidism (see Chapter 15).

Therapy includes strict cage rest to prevent more damage and normalization of the diet. Cage rest should be

Table 10.6. Plasma Levels of Calcium, Phosphorus, and the Major Vitamin D Metabolites in Small Breed Dogs Raised Under Normal Circumstances, or on a Diet Deficient in Calcium or Vitamin D

	Calcium (mmol/L)	Phosphorus (mmol/L)	PTH (ng/L)	25-OHvitD (nmol/L)	$1,25(OH)_2vitD$ (pmol/L)	$24,25(OH)_2vitD$ (nmol/L)
Normal	2.8 ± .1	2.7 ± .1	20 ± 2	50 ± 5	95 ± 5	169 ± 44
Hyperparathyroidism	2.7 ± .1	2.7 ± .1	30 ± 1 $^{\otimes}$	77 ± 22	494 ± 87 $^{\otimes}$	45 ± 29 $^{\otimes}$
Hypovitaminosis D	2.7 ± .1	2.0 ± .3 $^{\otimes}$	>35 $^{\otimes}$	6.2 ± .2 $^{\otimes}$	65 ± 5 $^{\otimes}$	1.4 ± .5 $^{\otimes}$

$^{\otimes}$ = significantly different from normal.

Plasma concentration of calcium, phosphorus, parathyroid hormone (PTH), 25-hydroxycholecalciferol (25-OHvitD), calcitriol [$1,25(OH)_2vitD$] and $24,25(OH)_2vitD$ in 3-month-old dogs raised on a balanced food ["normal": Ca 1.1%, P 0.9% (DM), vitamin D 500 IU/kg food], on a food with low Ca content ["hyperparathyroidism": Ca 0.05%, P 0.9% (DM), vitamin D 500 IU/kg food], or on food without vitamin D ["hypovitaminosis D":Ca 1.0%, P 0.9% (DM), vitamin D not added to semi-synthetic food] (Hazewinkel and Tryfonidou 2002).

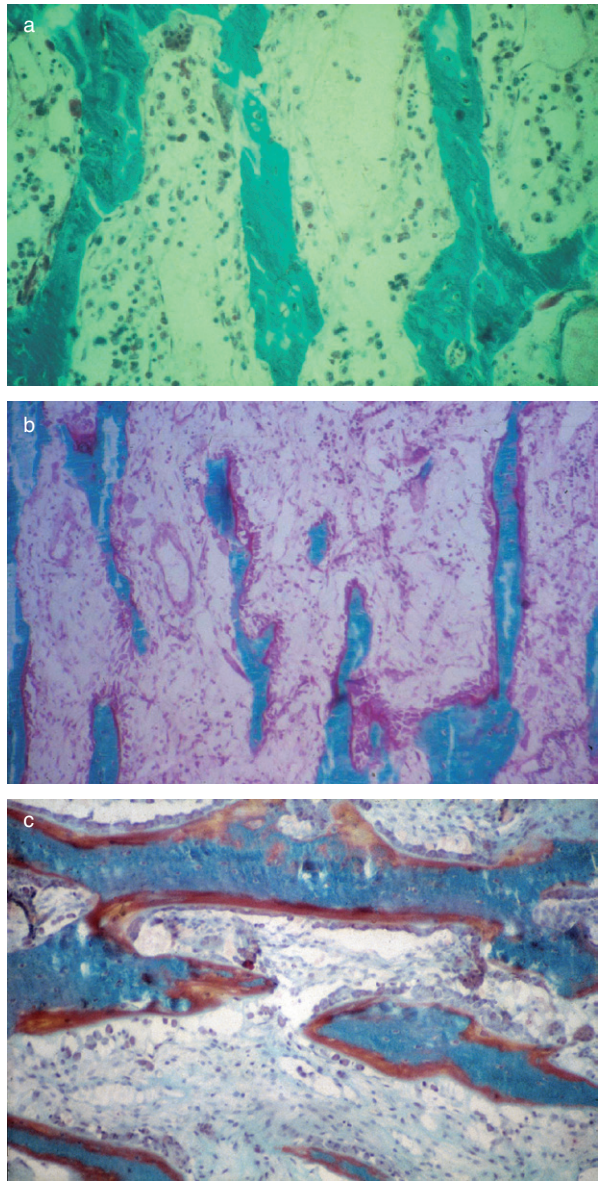


Fig. 10.3. (a) Cancellous bone of the epiphyseal area of a 6-month old dog. (b) Cancellous bone in the corresponding area of a 6-month-old dog with nutritional secondary parathyroidism due to low calcium content of the food (0.55% Ca on dry matter basis). Notice the large amount of osteoblasts and osteoclasts causing high bone turnover, active in new bone formation and bone resorption, respectively, responding to the hypocalcemia induced high PTH level. Thinned bone will break (greenstick fracture) and collapse (compression fracture). (c) Cancellous bone of a 6-month-old dog with hypovitaminosis D. Notice the red seams of osteoid (equal to nonmineralized collagen formed by osteoblasts) covering the mineralized bone, and multinucleated osteoclasts, not able to reach the mineralized bone. The latter will cause, together with the inability to absorb Ca and P in the intestine, a gradual decrease in plasma calcium and phosphorus levels.

started immediately to prevent other bones from fracturing, especially vertebral collapse and subsequent spinal cord damage, as well as to prevent further skeletal malformations. Normalization of the diet can be accomplished by changing the food to a complete and balanced diet and extra calcium carbonate (50 mg calcium per kg body weight per day) can be supplemented for 3 weeks. Injections of calcium are not indicated; the amount of circulating calcium is sufficient to prevent cardiac abnormalities. Extra vitamin D is not indicated in case of pure alimentary secondary hyperparathyroidism, since the endogenous $1,25(OH)_2vitD_3$ is increased by the high level of PTH (see the section on rickets). Therefore, calcium absorption is very efficient, i.e., up to 100% of the amount of calcium in the food, and thus extra vitamin D is contraindicated so as to not to further increase osteoclast activity (Nap, Hazewinkel et al. 1993b). The bone is too thin to consider orthopedic treatment of the fractures other than rest; even splints cannot be applied since the bone will break at the proximal margin of the splint. After mineralization of the skeleton, which is completed within a month, corrective surgery can be considered when indicated. The prognosis depends on the severity of secondary spinal cord damage and the severity of skeletal malformation, especially narrowing of the pelvis canal with disturbed passage of the feces.

Phosphorus Deficiency

An absolute deficiency of dietary phosphorus rarely occurs in companion animals; however, a relative deficiency may occur in extreme cases. When providing a food with very high calcium content to puppies less than 2 months of age, insoluble and thus nonabsorbable calcium-phosphorus salts are formed in the intestinal track. Due to the excess of dietary calcium there is a hypercalcemia with negative feedback on PTH synthesis and thus decreased $1,25(OH)_2vitD$ synthesis. The increased calcium absorption in these young dogs consuming diets with excessive calcium (Schoenmakers et al. 2000) will cause hypercalcemia. Both the hypophosphatemia and the lack of $1,25(OH)_2vitD$ will cause a disturbance in skeletal mineralization, resulting in wide growth plates and thin cortices evident on radiographs.

The diagnosis can be made from the diet history, radiological investigation, and laboratory findings. Hypercalcemia and hypophosphatemia together with hypoparathyroidism and decreased hydroxylation of vitamin D will coincide with the radiological signs as seen in rickets (Schoenmakers et al. 2000), commonly referred to as hypophosphatemic rickets. (Fig. 10.4).

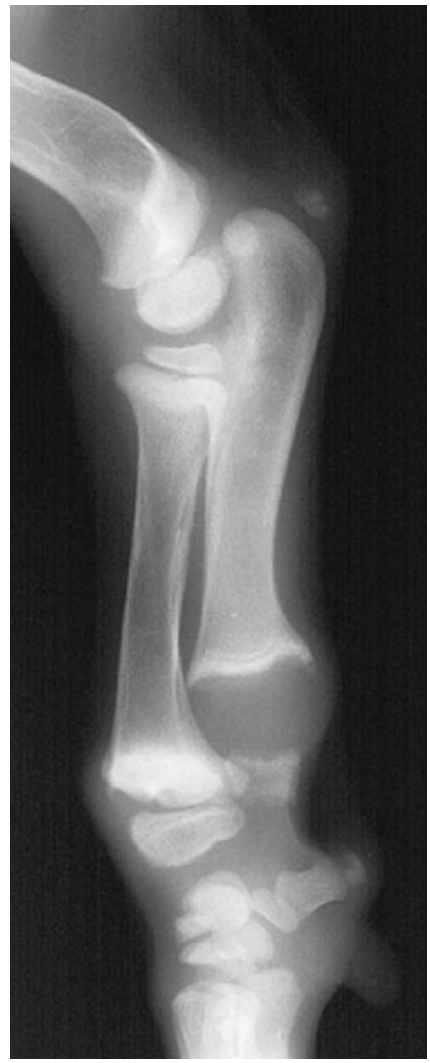


Fig. 10.4. Hypophosphatemic rickets. Great Dane of 2 months raised on food with 3.3% calcium on dry matter basis starting at 3 weeks of age with hypophosphatemia and thus disturbed bone and cartilage mineralization. Notice the poor contrast between bone and soft tissue and the mushroom appearance of the (nonmineralized) growth plate. The radiological signs do not differ from dogs with hypovitaminosis D (= rickets).

Vitamin D Deficiency (Rickets or Hypovitaminosis D)

The ability to synthesize cholecalciferol in the skin under the influence of ultraviolet light has been developed in amphibians, reptiles, birds, herbivores, and omnivores, but not in dogs and cats (How et al. 1994). The cutaneous level

Table 10.7. Vitamin D Recommendations for Growing Dogs

	Vitamin D content per kg food (dry matter)
National Research Council Nutrient Requirements of Dogs and Cats (2006)	552 IU* (4,000 kcal ME/kg diet)
Meyer (1983)	500–1,000 IU
Association of American Feed Control Officials (AAFCO) (2011)	500 IU** - (4,000 kcal ME/kg diet)

*Recommended allowance.
**AAFCO minimum.
1 µg cholecalciferol = 40 IU vitamin D.

of the vitamin D_3 precursor 7-dehydrocholesterol (7-DHC) is low due to a high level of 7-DHC reductase, an enzyme with a high activity that converts 7-DHC into cholesterol (Morris 1999). Thus dogs and cats are solely dependent on dietary sources to meet their vitamin D requirement. Animal fat has high levels of vitamin D; vegetarian food and lean meat (like poultry) have low levels of vitamin D. Commercially available dog and cat food does not need any vitamin D supplementation, regardless of the season or the latitude, especially because vitamin D content is in most cases above the recommended daily requirement (Table 10.7).

Dietary vitamin D is absorbed in the intestine by passive diffusion, transported in plasma bound to chylomicrons, lipoproteins, and vitamin D-binding proteins (DBP), and routed to the liver where 40–60% will be absorbed and 25OHvitD_3 is formed. In the kidneys, further hydroxylation results in 1,25$(OH)_2$vitD_3 and 24,25$(OH)_2$vitD_3, which appear in the plasma, whereas hydroxylation at other sites (like the intestine, growth plates, and placenta) is not reflected. A variety of factors, related to breed, age, and dietary composition, influences the plasma concentrations of these main metabolites.

Since the main role of 1,25$(OH)_2$vitD_3 is mineralization of newly formed cartilage and osteoid, hypovitaminosis D (i.e., rickets) in young growing animals is radiologically characterized by wide growth plates (this is contrary to alimentary hyperparathyroidism), and by thin cortices with possibly curved bones and/or greenstick fractures [Fig. 10.2]. Histological investigation of bone biopsies will also reveal broad (unmineralized) osteoid seams [Fig. 10.3(c)], formed by a large amount of osteoblasts, whereas osteoclasts are seldom attached to mineralized bone. The diagnosis can be confirmed by laboratory investigation. Hypocalcaemia is secondary to decreased intestinal calcium absorption and bone resorption, which will cause hyperparathyroidism and hypophosphatemia due to the same causes as the hypocalcemia plus the hyperparathyroidism-induced hyperphosphaturia. The plasma concentrations of the vitamin D metabolites (especially 25OHvitD_3 and 24,25$(OH)_2$vitD_3) will be very low, whereas 1,25$(OH)_2$vitD_3 may be in the low-normal range (Table 10.6).

Rickets is only seen under extreme circumstances including unsupplemented homemade foods, in dogs with an inability to absorb fat and thus also vitamins soluble in fat, and in cases of inborn errors of vitamin D_3 metabolism. Treatment includes normalization of the diet. In cases where vitamin D deficiency is the only abnormality, vitamin D supplementation up to 500 IU per kg body per day is sufficient. In most cases the daily requirements of a variety of nutrients, vitamins, and minerals will not be met, and thus a complete, balanced commercially available dog or cat food should be advised.

In 3 weeks, restoration of the skeleton can be noticed since cartilage and osteoid are waiting to become mineralized. After complete mineralization of the cortices and callus formation occurs around the fractures, orthopedic correction can be performed when indicated.

Inborn errors of vitamin D metabolism are resistant to even prolonged vitamin D therapy; treatment with calcitriol (which warrants careful monitoring of plasma calcium and phosphorus levels) can be indicated until the skeleton is normally mineralized and growth is completed. Calcitriol can then be discontinued in order to avoid abnormal mineralization or stone formation.

Deficiency of Other Trace Minerals

In an extreme situation, such as feeding a home-prepared diet based solely on potatoes, milk products, and cereals without supplementation, it is possible that a deficiency in one of the trace minerals such as copper, zinc, or manganese might develop, resulting in subsequent disturbances in skeletal development. It can be anticipated that an excess of calcium might also cause a deficiency in other bivalent ions like copper and zinc, although this has yet to be reported (Zentek and Meyer 1991).

Calcium Excess (Alimentary Hypercalcitoninism)

The calcium requirement will differ largely for different growing animals, depending on their growth rate. Meta-analysis revealed that the relationship between true calcium absorption (as determined with the aid of calcium tracer studies)

during the first 6 months of life was directly proportional with the calcium content of the food (i.e., intake$^{0.82}$, with dietary calcium ranging from 0.33–3.3 g per 100 g food on a dry matter basis), but independent of breed (Tryfonidou, van den Broek et al. 2002). Evolution of terrestrial mammals has been directed to a calcium-deficient environment; young animals with a very functional paracellular, passive absorption of calcium cannot refuse an excess of dietary calcium. This is unlike mature animals, where the paracellular pathway has been sealed in a way that calcium and other molecules cannot diffuse through the intestinal wall.

Feeding an excess of calcium to young, large breed dogs is common practice by many owners concerned about the skeletal diseases described above. For that reason, owners supplement dog food with minerals to prevent calcium deficiency. The addition of 2 tsp of calcium carbonate to a balanced diet of a 3-month-old, fast-growing dog will almost double the daily calcium intake and thus double its calcium absorption. The source of calcium—bone meal, fresh bones, or dairy products—does not make a lot of difference; it is the amount of calcium eaten and absorbed that counts. Manufacturers in their effort to produce a food for all breeds and all life stages enrich their foods with plenty of calcium. Feeding a 3-month-old, fast-growing dog an adult maintenance diet (320 kcal/100 g; 1.6% Ca DM) instead of a puppy diet (420 kcal/100 g; 0.8% Ca DM) with a daily requirement of 2,700 kcal will consume 5.1 g of calcium with the puppy food and 13.5 g of calcium with the adult maintenance diet. In addition, meat and bone meal as a source of protein is used in some complete foods, thus providing both protein and an excess of calcium at the same time. This information can be hidden behind the expression of "minimal content" instead of the actual content on the label. Calcium content above 2.5% in dry and canned mixed products is no exception (Kallfelz and Dzanis 1989).

High calcium intake will cause hyperplasia of calcitonin (CT) producing C-cells and thus an increased response in calcitonin following calcium absorption during a meal, even months after normalization of the calcium content of such a meal (Fig. 10.5) (Schoenmakers et al. 2000). The CT-depressed osteoclast activity will lead to decreased bone remodeling with consequences for blood vessels running through the cortex of long bones. Great Dane puppies nourished by the bitch and given a high-calcium diet (3.3% calcium on DM) only between the ages of 3 and 6 weeks (i.e., in the period of partial weaning) had an increased CT-response and an increase in plasma Ca concentration until 17 weeks, and in all these dogs radiologically confirmed enostosis (panosteitis eosinophilia) (Fig. 10.6) was diagnosed, but not in the (control) Great Danes

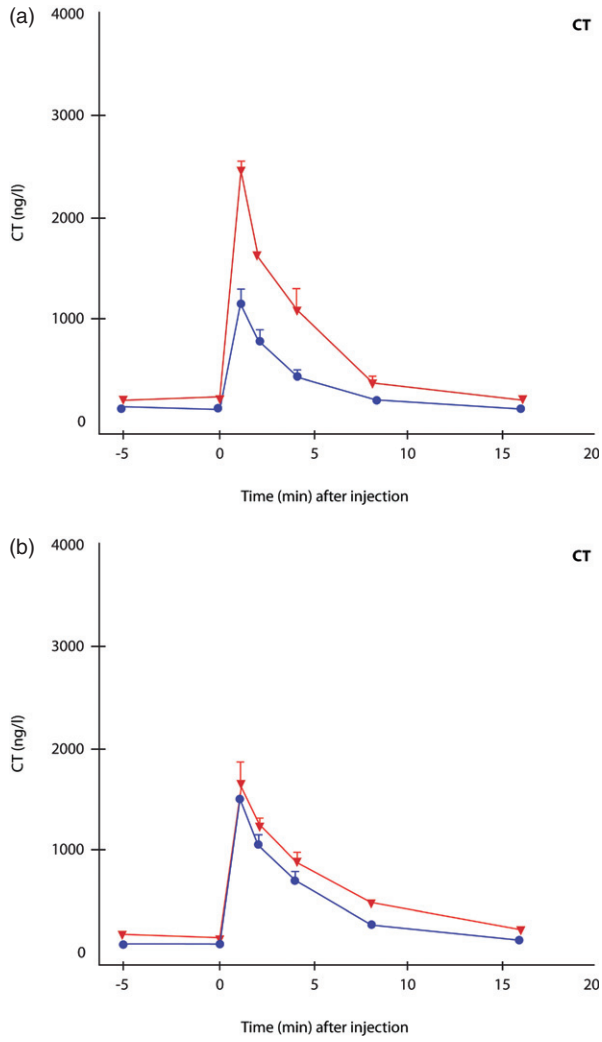


Fig. 10.5. Alimentary induced hypercalcitoninism. Two groups of Great Danes, raised on food (as a gruel from 3–6 weeks) only differing in its Ca content, i.e., 1.04 (n = 9, blue) and 3.11 (n = 5, red) g per 100 g dry matter food (both with phosphorous equal to 0.85 g and vitamin D equal to 110 IU per 100 g DM) starting at 3 weeks of age. From 6 weeks onward, both groups received the food with Ca content of 1.04% from 6 weeks till 6 months of age. At time point 0, Ca-bolus iv-injection (2.5 mg Ca per kg bw) was given, and the calcitonin (CT) plasma concentrations were determined at the time points as indicated at the age of (a) 13 and (b) 26 weeks. Notice the increased basal level and response even seven weeks after normalization of the food, with a normalized response at 26 weeks of age. See "alimentary hypercalcitoninism" for clinical relevance (Hazewinkel et al. 2000).

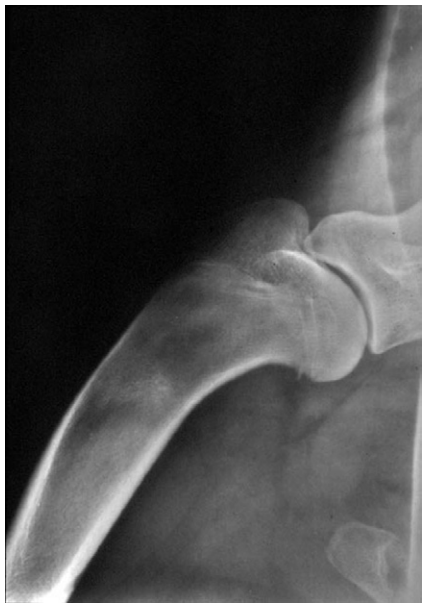


Fig. 10.6. Inside the medullary cavity, white confluating spots are visible, indicating areas of mineralization, as radiological signs of panosteitis, which is clinically characterized by shifting lameness, varying in severity and location with pain reaction upon deep palpation of the long bones.

raised on food containing 1.1% calcium (DM) from 3 to 17 weeks of age (Schoenmakers et al. 2000). So a high calcium intake for a short but crucial period in life, and only in addition to the bitch's milk, can have major consequences in later life. Although multiple hypotheses are proposed to describe the etiopathogenesis of panosteitis, no other dietary cause has been found thus far (Hazewinkel, Nap et al. 2000).

The clinical signs (shifting lameness of differing severity, and pain upon deep bone palpation) together with the radiological signs (white confluent areas within the medullary cavity, starting near the nutrient foramen) in young dogs of large breeds until the age of 24 months is strong evidence for this disease. The treatment is to prescribe a diet with a calcium content matching the requirement (with possibly a 3-week period of calcium deficiency to induce skeletal remodeling) together with nonsteroidal, anti-inflammatory drugs to help the animal overcome painful periods until the age of 24 months. In order to prevent panosteitis, a diet designed for young dogs of large breeds with a calcium content no greater than 1.1% on a dry matter basis should be fed during the growth period, starting at partial weaning.

Chronic calcium excess can result in a decreased widening of the foramen for blood vessels and the spinal cord. Great Danes provided free access to food (Table 10.5) (Hedhammar et al. 1974; Lavelle 1989) or limited intake of food but with a high calcium content (3.3% Ca on a dry matter basis) (Hazewinkel, Goedegebuure et al. 1985) had narrowing of the cranial aperture of the cervical vertebral bodies causing wallerian degeneration of the spinal cord and the typical signs of wobbler syndrome: ataxia and crossed extension reflexes. With imaging techniques, narrowing of the spinal canal without herniation of the nucleus pulposus can be detected. Surgical techniques may be indicated although the damage to the nerve tissue may already be irreversible. Dietary corrections and medical treatment are often too late to have any impact. Differential diagnoses include vertebral or spinal cord malformations, cervical vertebral instability as seen in older dogs, discospondylitis, and meningitis.

High calcium intake will have a tendency to cause the calcium level to increase and therefore increase CT secretion and suppress PTH secretion, and 1α-hydroxylase formation lowering $1,25(OH)_2$vitD synthesis. The increase of CT and the lowering of PTH as seen in large breed dogs may be the cause of the high incidence and severe signs of osteochondrosis in young dogs raised on a diet with a high calcium content. Support for this comes from the finding that the influence of high calcium intake did not decrease PTH levels significantly in young dogs of small breeds (Nap, Mol et al. 1993). In this study, Great Danes, but not Miniature Poodles, raised on diets with a high calcium content or with an increased calcium and phosphorus ratio, had severe signs of retained cartilage cones (considered to be osteochondrosis of the growth plates) with radius curvus as a consequence, i.e., elbow incongruity, bowing of the radius, and valgus deformation of the front and rear feet (Hazewinkel, Goedegebuure et al. 1985; Schoenmakers et al. 2000) (Fig. 10.7). These Great Danes developed osteochondrosis at typical locations in joint cartilage. In some cases, where Great Danes were raised on a diet with excess calcium, it was not the distal growth plate of the ulna that was the most affected but the growth in length of the radius resulting in incongruity of the elbow with a shortened radius (Hazewinkel, Goedegebuure et al. 1985; Schoenmakers et al. 2000).

Vitamin D Excess

Vitamin D is an essential vitamin in dogs and cats, since it cannot be synthesized in these species in their skin under the influence of sunlight (How et al. 1994). Since it is

Fig. 10.7. Four-month old Great Dane, with radius curvus syndrome raised on a food with calcium excess.

soluble in fat and transported to the liver for hydroxylation, the nutritional content of vitamin D is connected to the fat and liver content of the ingredients. In balanced dog foods, the raw ingredients are supplemented with vitamin D together with other essential nutrients by the manufacturer in the vitamin premix. As a result, the available diets for companion animals can have a vitamin D content exceeding recommended levels (Table 10.7).

Dogs raised on a diet containing a 135-fold increase of the recommended dietary vitamin D content [54,000 vs. 4,560 IU cholecalciferol per kg diet, which corresponds with a mean (±SD) of 1615 ± 60 vs. 15 ± 1 IU vitamin D per kg body weight per day] starting at the age of 6 weeks demonstrated an adaptation mechanism through which the increased hydroxylation of excess vitamin D occurred in both 25OHvitD and $1,25(OH)_2$vitD, without signs of increased calcium absorption or pathological mineralization as is commonly seen in vitamin D intoxication. This adaptation mechanism results in increased plasma concentrations of $24,25(OH)_2$vitD and decreased levels of $1,25(OH)_2$vitD, with severe disturbances of endochondral ossification as a consequence resulting in retained cartilage cones at the age of 15 weeks, and eventually radius curvus syndrome (Fig. 10.7). In dogs raised on an excess of vitamin D alone, the disturbed endochondral ossification cannot be explained by a direct influence of calcium on maturing chondrocytes. However, in these dogs, plasma levels of PTH were significantly decreased and CT was significantly increased when compared with controls, which mimics the situation as described under "calcium excess." This suggests that osteochondrosis is caused in these dogs by an imbalance in calciotropic hormones and/or adaptations in the vitamin D metabolism, generalized or locally at growth-plate level, rather than due to high calcium levels per se (Tryfonidou, van den Broek et al. 2002).

Chronic vitamin D intoxications due to ingestion of rat poison or due to excessive dosages of vitamin D or its metabolites will be characterized by hypercalcemia, hyperphosphatemia, muscle weakness, nausea, kidney failure, and possibly death. Chronic intake of 10,000 IU per kg body weight per day or a single dose of 200,000 IU per kg body weight results in clinical signs including polyuria and vomiting (Spangler et al. 1979).

Vitamin A Excess

Vitamin A is essential in bone metabolism and influences chondrocyte proliferation, and osteoblast and osteoclast activity, in addition to a variety of other functions. Vitamin A ($C_{20}H_{29}OH$) is present in animal fat and can, in dogs but not in cats, be synthesized out of β-carotene ($C_{40}H_{56}$) by cleavage with the aid of carotenase, as present in the intestinal mucosa and liver cells. Therefore, the dietary requirement of vitamin A for cats is higher than for dogs. Another difference between dogs and cats regarding vitamin A metabolism is in its inactivation; dogs, but not cats, can form retinyl esters to inactivate vitamin A, and dogs are able to excrete 15–60% of the daily intake as retinyl palmitate in the urine. Cats absorb all the vitamin A from food ingredients that contain retinol and retinyl esters, and although this could induce vitamin A toxicity, cats can sequester larger quantities of vitamin A in the liver with no apparent adverse effect. In addition, cats form retinyl stearate out of retinol and low-density lipoproteins. No apparent deleterious effects were caused by high intakes of vitamin A alone. Adult cats, even after a period of 3 years on 50 and 100 times the control cats (on 6 mg retinol equivalents) did not develop pathological signs (Morris 2002).

Hypervitaminosis A can be caused in kittens and puppies after several weeks of oversupplementation. Such kittens and puppies will have reduced growth in length and osteoporosis of long bones together with flaring of the metaphyseal regions. Hypervitaminosis A in dogs results in anorexia, decreased weight gain, narrowing growth plate cartilage, new bone formation, and thin cortices. Concentrations of vitamin A in plasma will exceed the normal ranges for dogs (i.e., 1,800–18,000 IU/L) (Hayes 1971).

Hypervitaminosis A is seen more frequently in cats than in dogs, especially in cats at an older age (3 to 13 years) and fed raw liver and/or fish daily. Hypervitaminosis A in cats may coincide with a stiff neck and/or enlarged joints from the front and hind legs (mainly elbow and stifle joint) due to ankylosis, dull hair coat, change in character (probably due to hypersensitivity and/or bone pain), anorexia, and weight loss (Hazewinkel 1994).

The recommended concentration of vitamin A in dog foods is 1,515 ug or 5,050 IU per kg dry matter with a safe upper limit 10 times this amount (NRC 2006). In dogs, a history of diet supplementation with cod liver oil may help to make the diagnosis. In cats, the history can indicate a prolonged preference for raw fish, raw liver, or supplements, although this is not always the case. In a study in adult cats, a 10^6 IU vitamin A per kg diet failed to produce the classic skeletal signs of hypervitaminosis A in 3 years' time, suggesting an individual predisposition (Morris 2002). The clinical and radiological signs can support the diagnosis. In addition bone biopsies can be taken, but a more easily obtained liver biopsy will show fatty infiltration. Laboratory investigation may reveal that retinol levels in the liver are increased, contrary to plasma retinol levels, which can be normal, as shown in a study where 20% of cats with hypervitaminosis A had normal plasma levels (Morris 2002).

Therapy should be started as soon as the diagnosis is made, including analgesia and food adaptation. It may be better to have a board-certified veterinary nutritionist formulate a balanced homemade diet without vitamin A added to it, since all commercially available foods contain at least the required amount of vitamin A (Hazewinkel 1994).

A low dose of nonsteroidal anti-inflammatory drugs can be provided to relieve the skeletal pain and pain due to any nerve entrapment. Since cats with hypervitaminosis A may have hepatic lipidosis, the dosage of analgesia may need to be reduced. General improvement can be seen 4 weeks after starting treatment; although ankylosis will not disappear, the cats may remain lame, but this is not due to pain.

NUTRIENT REQUIREMENTS FOR SKELETAL MAINTENANCE IN ADULT ANIMALS

In the adult dog under balanced conditions, both mineralization of the skeleton and bone resorption are 4–8 mg/ kg body weight per day, which is almost 100 times less than in young, fast-growing dogs (Hazewinkel 1989). Endogenous fecal excretion (i.e., losses of calcium via bile or mucosal cells) is approximately 10–30 mg/kg and urinary losses approximately 1–7 mg/kg body weight per day. The losses can be compensated for by an intake of 50 mg calcium per kg body weight per day. But even when this is not reached, the skeleton represents such a large reservoir of calcium that losses can be compensated for by an increase in bone resorption. Pathological fractures in adult dogs or cats do not generally occur secondary to an unbalanced diet but rather under strenuous physiological conditions such as gestation and lactation without adequate compensatory food intake.

Unlike postmenopausal humans, dogs do not increase bone resorption after loss of ovarial hormonal influences. Working dogs may lose extra calcium with saliva but this is only a limited amount and hardly requires any compensation.

The major clinical problems in relation to orthopedics in adult companion animals are excessive energy intake (see below), excessive phosphorus intake together with decreased renal function, and excessive vitamin A intake, especially in cats (see above).

In the case of renal insufficiency, both in young and in adult dogs, calcium is lost in the urine whereas phosphorus is insufficiently excreted, resulting in sequestration of calcium intracellularly as calcium phosphates and at different locations with increased pH values (lungs, stomach, and kidneys), thereby lowering the plasma calcium concentration even further. This will cause a hyperparathyroidism (i.e., renal secondary hyperparathyroidism) with increased osteoclast activity causing demineralization of the skeleton. An increase in calcitriol formation under the influence of high PTH levels helps to increase intestinal calcium absorption, but the hydroxylation of 25OHvitD in the kidney is often disturbed in the case of chronic renal insufficiency. Although PTH will lower the threshold for phosphorus in the kidneys and thus will increase renal phosphorus excretion, this mechanism is also disturbed in chronic renal failure. Dietary phosphorus restriction will keep the plasma phosphorus level in the normal range until renal function becomes inadequate. Due to the high turnover in cancellous bone, bone pathology is often initially seen clinically as severe bone loss in the jaws. Loosening of teeth and lowering of the arch can be noticed in adult dogs with chronic renal failure (i.e., hypostotic osteodystrophy), whereas hyperostotic osteodystrophy is characteristic for growing dogs with renal insufficiency (as is the case with hydronephrosis or other birth defects) (Fig. 10.8). In these young dogs, their noses are much broader than normal and the gingiva seems to be thickened, all due to compensatory growth of nonmineralized fibrous tissue, and the teeth are often loose. Clinical pathology will reveal

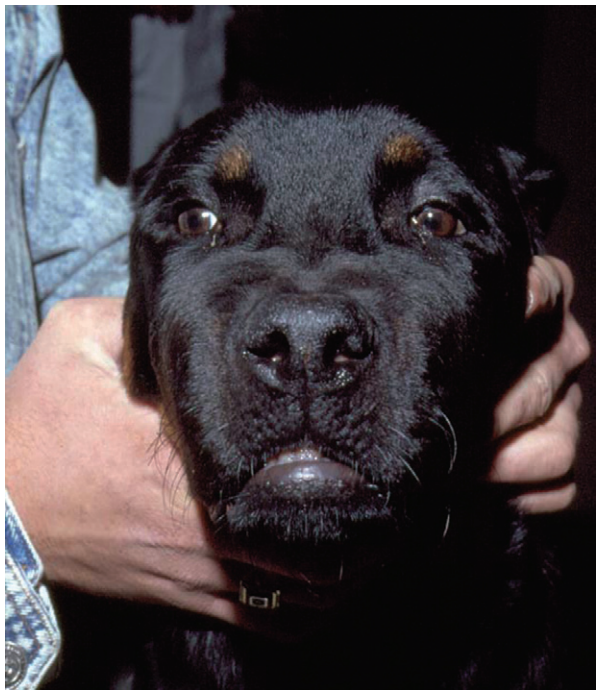


Fig. 10.8. Five-month old Rottweiler with poor renal function and hydronephrosis and broadening of the maxilla.

low to normal calcium; very high phosphorus, urea, and creatinine levels; and low 1,25(OH)2vitD_3 levels. Radiographs will show a loss of the lamina dura dentis and a loss of contrast in the skull compared to the teeth that do not lose their mineral content. Mineral loss of the skeleton is often irreversible together with the deteriorating general health of the patient.

IMPLEMENTATION OF NUTRITION IN CLINICAL ORTHOPEDICS

There are numerous foods available on the commercial market, making it impossible to comment on each food. It should be recognized that the driving force of food intake in each individual, especially growing dogs, is the need for energy. Together with energy come the essential nutrients for skeletal growth, including calcium, phosphorus, and vitamin D. In addition to the requirement per kg body weight of growing dogs, the expression of these elements on an energy basis (kcal/kg diet) is also common, although more active dogs need more energy but not necessarily more minerals (i.e., calcium and phosphorus). Owners feed their dogs more often on a weight or volume basis rather than calculating the energy intake. When a diet is calculated for a growing dog of a certain body weight, the amount should be regularly adjusted as the dog becomes heavier as it matures. This can be done through consultation with a veterinary nutritionist. One must account for not only the chemical composition but also the availability and the biological value of the nutrients in the diet. It is virtually impossible to judge the quality of a diet from the label. A diet with a high grain and phytate content may need a higher calcium level to provide the required calcium for absorption and a higher phosphate content since the phosphate in phytate is not absorbable. This may explain why a meta-analysis reported that at 2 months of age, 260–830 mg calcium per kg body per day appears to be safe for skeletal growth; decreasing to 210–540 mg calcium per kg body per day at 5 months of age (Fig. 10.1) (Hazewinkel and Mott 2006). To stay away from all these confusing figures, it is advised that young dogs be raised on a diet formulated for the growth and special hormonal typicalities of the breed. Small breed dogs undergo a slow growth rate and therefore have a wide safety margin to deal with nutrient concentrations above or below the dog's requirements. Giant breed dogs with their balanced, but vulnerable, equilibrium of hormonal regulators do not reveal this safety margin. Couple this with the inherited developmental diseases such as hip and elbow dysplasia with a large degree of environmental influence, including nutrition, and one can understand the importance of educating the breeder and new owner of young, large breed dogs that they should be fed a diet adapted to their special needs, i.e., a calcium content at the lower end of the safety spectrum. In general, in foods with a protein content of high biological value, the calcium content should be between 0.8% and 1.0% on a dry matter basis (for a food with 4.2 kcal/g diet). This range is present in the diets of the major dog food manufacturers but still not seen in many smaller brands and in diets supplemented by owners themselves.

In summary, skeletal growth is limited to endochondral ossification, periosteal growth, and remodeling with a limited amount of cell types. These cells are working under the influence of different growth factors of which they have the calciotropic hormones (PTH, vitamin D, CT) in common. Calcium as a vital mineral will be regulated in plasma as tight as possible under all circumstances, including rapid growth and extreme calcium (and vitamin D) intakes. The adaptation mechanisms to maintain calcium homeostasis may have consequences for the maturing skeleton and thus for later life. A thorough understanding of the pathophysiological mechanisms and thus

recognition of different expressions of the same disturbance (greenstick and compression fractures, osteochondrosis, radius curvus syndrome, and wobbler syndrome) will help give guidance to the nutritional prevention (and at times treatment) of generalized skeletal diseases in breeds at risk.

INFLUENCE OF NUTRITION IN THE OCCURRENCE OF ORTHOPEDIC DISEASES

Elbow Dysplasias

Elbow dysplasias (EDs) are a serious problem for certain populations. EDs can be separated into different disease entities including ununited anconeal process (UAP), fragmented coronoid process (FCP), osteochondritis dissecans (OCD) of the medial humeral condyle, and incongruities of the elbow joint (INC) [Fig. 10.9(a)]. EDs should be considered as different diseases, which may all cause lameness and which may all cause osteoarthritis (OA) of the elbow joint [Fig. 10.9(b)].

Depending on the specific subpopulation and the method of investigation, EDs are seen in 46–50% of Rottweilers, 36–70% of Bernese Mountain dogs, 12–14% of Labrador Retrievers, 15–20% of Golden Retrievers, 30% of Newfoundlands, and 18–21% of German Shepherd dogs, and in many other breeds (Temwichitr et al. 2010). The clinical investigation starts with determination of the breed (see above) and age at which the first signs appeared, most typically between 4 and 10 months. The elbow is often effused on palpation, the range of motion can be decreased, and subtle crepitation can be recognized. Diagnosis of EDs can be confirmed by radiographs in most cases by demonstrating the primary disease (UAP, OCD, INC, and in certain cases even FCP), or secondary changes as part of OA development, taking into account the osteophytes and sclerosis of the semilunar notch in making the diagnosis [Figs. 10.9(a) and 10.9(b)]. Most instances of EDs occur bilaterally in 30–70% of the cases, and therefore both elbow joints should be investigated, even in cases of unilateral lameness. In cases where there are no radiographic abnormalities in dogs with clinical lameness, and other causes of front leg lameness are excluded (including panosteitis, OCD in the shoulder joint, sesamoid fractures, and biceps tendon pain) auxiliary techniques including computed tomography, bone scintigraphy, and arthroscopy can be of value.

Early surgical intervention provides the best prognosis for the future status of the joint in lame dogs, although some experts advocate a more conservative approach. The ununited anconeal process can be removed, or reattached in instances of partial or acute detachment. When cartilage of the medial humeral condyl is unattached in cases of OCD, or when the apex of the coronoid process is fractured in cases of FCP, the loose bodies are removed. When fissures are present in the apex of the medial coronoid or cartilage is weakened due to chondromalacia, the apex should also be removed. INC due to a short radius is frequently seen in Bernese Mountain dogs and in dogs raised

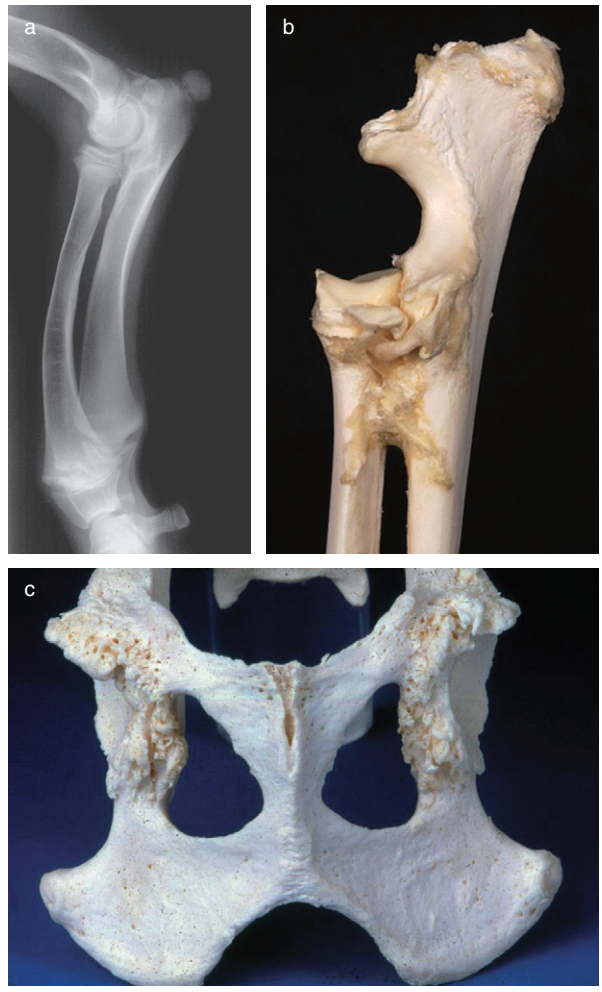


Fig. 10.9. Radiograph and pathological specimen revealing: (a) incongruity (too short radius) of the joint in a Great Dane raised on food with increased calcium and phosphorus content (Schoenmakers et al. 2000). (b) Osteoarthritis of the elbow joint, notice the shortened radius and the dislocated medial coronoid process. (c) Osteoarthritis of the hip joint due to hip dysplasia characterized by osteophyte formation and cartilage breakdown.

on food supplemented with excess minerals. Congruity is restored after the removal of the FCP or UAP at the same surgical intervention. The prognosis ranges from good in cases with minimal cartilage damage to poor in cases of severe OA (Innes 2009).

Role of Nutrition in EDs

A combination of FCP and OCD have been described by Olsson (1993) as a disturbance of endochondral ossification and as such expressions of the same disease. Although this may still be true in cases of chondromalacia, in the other forms of FCP (loose apex or fragmentation) primary mechanical overload of subchondral bone or joint cartilage is considered as the primary cause (Wolschrijn and Weijs 2004). OCD and FCP are seen more frequently in certain breeds and certain subpopulations with a chi-square of less than 0.3, suggesting a considerable influence of environmental factors including nutrition. It has been demonstrated in well-controlled studies that endochondral ossification can be disturbed by high food intake (Hedhammar et al. 1974; Lavelle 1989) and excessive calcium intake (Hazewinkel, Goedegebuure et al. 1985; Schoenmakers et al. 2000) as well as by oversupplementation of a balanced diet with vitamin D (Tryfonidou, Holl, Vastenburg et al. 2003). Protein-rich rations have not been shown to have a disturbing influence on skeletal development (Nap, Hazewinkel, Voorhout et al. 1991). In a study in Great Danes raised on food with an increased calcium and phosphorus intake (3.3 and 3.0%, respectively, compared to controls on 1.1% and 0.9%, respectively) starting at the age of weaning (i.e., 3 weeks of age) until 17 weeks, the dogs developed disturbances in endochondral ossification in the growth plates of the distal radius and/or ulna. As a consequence, elbow incongruity developed either due to a severe disturbance of growth in the length of the radius or due to a severe radius curvus syndrome with disturbed growth in the length of the ulna (Hazewinkel, Goedegebuure et al. 1985; Schoenmakers et al. 2000). The former may coincide with overloading and thus fracturing of the medial coronoid process, while the latter may coincide with an UAP or the painful pressure of the humeral condyle against the UAP, all leading to OA of the elbow joint.

In a study in Labrador Retrievers it has been shown that OA in multiple joints (including hips, elbows, and shoulders) developed in overweight dogs and less frequently in restrictively fed, slim littermates (Kealy, Olsson et al. 1992; Huck et al. 2009). The frequency and severity of the occurrence of disturbances in endochondral ossification as a common factor in EDs can be decreased in breeds at risk by dietary management, including the feeding of a diet with an appropriate calcium-to-energy ratio, a quantitative restriction of energy intake, and by not adding vitamin D to a balanced diet.

Hip Dysplasia

Although much is known about the symptoms and treatment modalities, little is known about the aetiology of hip dysplasia (HD) in dogs. Symptoms include laxity of both hip joints (Bardens and Hardwick 1968), with an increased pressure load on the joint surface causing cartilage disruption of the acetabulum and femoral head and eventually deformity of the joint and increased bone formation in the subchondral area [Fig. 10.9(c)]. Pain is the dominant clinical sign during the first phase of HD with reluctance to play and walk, whereas in the advanced stages OA symptoms dominate (i.e., stiffness after rising, warming out, inability to move the joint in a normal range). Laxity of the hip joint is a constant feature in HD. The laxity can be controlled in the dog in lateral recumbancy, without or with anesthesia, by moving the femur in an upward direction. Originally this was performed at 4 weeks of age with a claimed error of 5%, although no follow-up was presented (Bardens and Hardwick 1968). Noticeable laxity begins to be evident at 4 months of age but becomes a more accurate predictor as the dog ages (Smith 2004; Vezzoni et al. 2005; Ginja et al. 2010). In mature dogs, laxity can also be evaluated clinically with the Ortolani and Bardens test, and radiologically by measuring the Norberg angle (Schawalder et al. 1998). Other radiological techniques may include enforced lateralization of the femoral heads with the aid of a fulcrum between the thighs as described by Smith (2004) and Vezzoni (2005), or by enforced craniodorsal pressure with abduction of the proximal femurs with the dog in dorsal recumbency according to Fluckiger et al. (1999).

In different studies the genetic influence of HD has been proven, although the chi-square indicates a strong environmental influence, including nutrition, activity, and perhaps other factors.

Nutritional Influences Seen in Hip Dysplasia

The collodiaphyseal angle (the angle of inclination) is approximately 135 degrees, but larger angles (coxa valga) are seen in conjunction with HD. In a longitudinal study in Great Danes raised on a food provided *ad libitum*, the angle between the collum femoris and the femoral shaft was larger than in the control group raised on a calorie-restricted, but similar, diet (Hedhammar et al. 1974). The increased energy (and thus also mineral) intake may have caused hypercalcitoninism with decreased osteoclast

activity and, as a consequence, hampered skeletal remodeling during maturation, with a more obtuse collodiaphyseal angle than the control dogs (Hedhammar et al. 1974).

The acetabulum is formed out of four ossification centers connected by cartilage fusions. During proportional growth of the femoral head, these ossification centers can drift away, thus remodeling during skeletal growth. Normally these ossification centers fuse at approximately 6 months of age. Asynchronous maturation of the head and acetabulum may be etiological factors in the development of poor joint conformation as present in HD. In a colony of fast-growing Labradors, fusion of the acetabular ossification centers occurred at 5 months of age resulting in more HD than in slower-maturing dogs (Lust et al. 1985). A disturbed development of the os acetabulare quatrum as a form of osteochondrosis causing OA of the affected hip joint has been described by Schawalder et al. (1998). Madsen et al. (1991) registered a delayed ossification of the femoral head during the development of hip dysplasia in large breed dogs. Late fusion of secondary ossification centers, together with severe osteochondrosis, has been described in Great Danes raised on food with increased calcium content (Voorhout and Hazewinkel 1987), suggesting a disturbance in endochondral ossification of the fusion of the acetabular bones in case of HD. This, together with mechanical overloading, may explain why overnutrition and thus fast growth is an etiological factor for the development of dysplastic hips (Hedhammar et al. 1974; Kasström 1975; Lust et al. 1985; Kealy, Olsson et al. 1992; Richardson et al. 2010). In addition, it may explain the involvement of multiple joints as reported in overweight dogs (Lust 1993; Kasström 1975; Kealy, Olsson et al. 1992). Interestingly, young dogs under 12 weeks of age with joint laxity did not develop hip dysplasia when raised on a low-caloric intake regime during growth (Richardson et al. 2010).

The dorsal acetabular rim (DAR) is cartilaginous until 3 to 4 months of age, and vulnerable to deformity in cases of joint laxity. The dorsocranial rim can develop from a separate ossification center by endochondral ossification (Morgan et al. 2000). This DAR can be visualized on radiographs with the X-ray beam parallel to the longitudinal axis of the pelvis. The line through the DAR should make an angle with the line horizontal through the pelvis (or perpendicular to the spinal processes) of <7.5 degrees (Slocum and Devine 1990) or even minus 1 or 2 degrees (Vezzoni et al. 2005). In case the angle becomes larger (i.e., the angle of inclination of the roof of the acetabulum becomes larger), the femoral head will have the tendency to slip outside the acetabulum. Constant lateralization of the femoral head plus increased production of synovial fluid may stretch the joint capsule and thus elongate it, allowing for subluxation of the femoral head. The round ligament, which connects the femoral head with the acetabulum, is far too long to keep the head inside the socket. In addition, the cartilaginous rim will erode, deform and even disappear, causing joint inflammation and irreversible malformation [Fig. 10.9(c)]. Also, acetabular filling and the presence of dorsal osteophytes can be noticed. Dorsal acetabular rim malformation can be caused by a disturbance in endochondoral ossification, especially in dogs that are overweight during growth. Hip dysplasia is called a biomechanical disease representing a disparity between primary muscle mass and disproportionately rapid skeletal growth (Riser 1993). The iliopsoas muscle, with its origin at the lumbar spine and pelvis and insertion on the trochanter minor of the femur, and the pectineus muscle, originating from the os pubis with insertion on the medial femur, can both subluxate the femoral head by becoming relatively shortened during fast skeletal growth (Bowen et al. 1972). In addition to selection for muscle strength, as has been proven in livestock genetics, muscle growth can be stimulated by protein intake. Nap, Mol et al. (1993) demonstrated that in Great Danes fed three levels of protein (31.6%, 23.1%, and 14.6% on a dry matter basis) in an isoenergetic, balanced dry dog food from 7 to 18 weeks of age, the group with highest protein intake had a more advanced body maturation reflected by a significant higher body weight without adiposities and without a difference in height or any skeletal abnormalities. Tvedten et al. (1977) could not detect an altered incidence of hip dysplasia in a study with a twofold elevation of dietary protein.

Synovial fluid is partly formed by the synovial membrane (mucine) and is partly a dialysate of plasma (the watery component). In the case of OA, inflammatory mediators cause vasodilatation with increased dialysis of plasma through the joint capsule and thus more and more watery synovial fluid than normal. It has been suggested by Kealy, Lawler et al. (1993) that a dietary anion gap (DAG) has a direct influence on the osmolality of the joint fluid, explaining the increased synovial fluid volume in hip joints of dysplastic dogs. However, the anion gap in the entire diet was not calculated and the absorbed ions were not measured, nor was the osmolality of the synovial fluid determined (Kealy, Lawler et al. 1993). Although the DAG may play a role, an increase in dialysate due to inflammatory mediators, including prostaglandins in cases of OA, seems to be a more likely explanation for the increase in fluid volume.

Overweightedness and obesity have been proven to enhance OA development due to overloading of the joint cartilage (Marshall et al. 2009) and possibly also due to hormonal influences. Labradors fed 30% more food than controls developed more frequent and more severe signs of OA in different joints including the hip joints. These overweight dogs had significantly higher IGF-I plasma levels and lower GH levels than controls (Hazewinkel, Kealy et al. 1999). These hormonal findings correspond to similar findings in overweight, postmenopausal women with thickened subchondral bone and loss of articular cartilage, resulting in severe OA. This, together with the decreasing water binding capacity of degradated proteoglycans in articular cartilage secondary to aging, may explain the increasing number of dogs, both overweight and lean, with OA at old age as reported by Kealy and Smith in a longitudinal study in Labradors (Smith et al. 2006).

In cases of severe OA with constant production of a superfluous amount of synovial fluid, the intra-articular pressure will increase and thus the joint capsule will be extended. Three months of cage rest combined with maintenance of a lean body weight has been demonstrated to improve ground reaction forces by 70% in dogs suffering from HD (Hazewinkel 1991). This is likely due to a decrease in joint inflammation allowing for restoration of cartilage damage and normalization of intra-articular pressure. A reduction in body weight, increased muscle force, chondroprotective agents, and nonsteroidal anti-inflammatory drugs have been proven or are expected to have a positive influence on the clinical outcome of medically managed cases (Ginja et al. 2010).

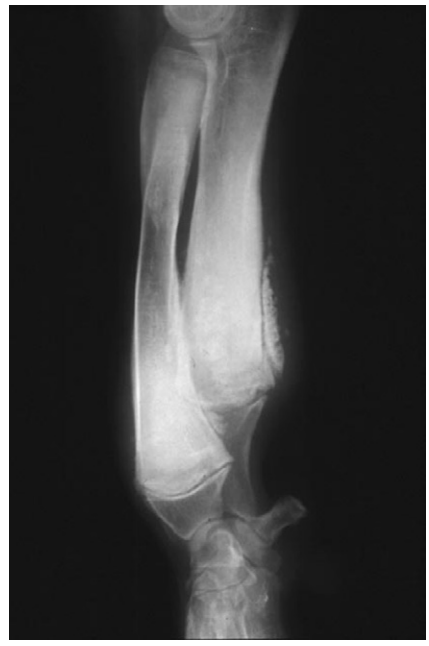


Fig. 10.10. Hypertrophic osteodystrophy (HOD) is characterized by a very painful episode, lasting approximately 3 weeks, followed by a slow rehabilitation with periosteal new bone formation in the metaphyseal area where a discontinuity of the bony tissue (pathognomonic for HOD) had been present.

Hypertrophic Osteodystrophy (or Metaphyseal Osteopathy) in Dogs

Hypertrophic osteodystrophy (HOD) is most commonly seen in Great Danes (with an odds ratio of 40) and other large breed dogs during their rapid growth phase (i.e., at 4 to 5 months of age). It is characterized by an inability to stand, fever, and malaise. Affected dogs are extremely painful at the metaphyseal areas of all long bones, especially at the distal antebrachium. The aetiology is obscure, and the disease has occurred in different studies in Great Danes overfed with minerals, including excessive calcium and phosphorus. Analogous to Paget disease in humans (Hoyland et al. 2003), particles of distemper virus have been demonstrated in osteoclasts in the area of increased osteoclasia. In cases of HOD, osteoclasia can be seen just 2–3 mm away from the growth plate, in the metaphyses (Mee et al. 1993). This is represented on radiographs by a black line, parallel to the growth plates at the early stage of the disease; in more advanced stages periosteal new bone formation leads to a bony cuff surrounding the zone of excessive bone absorption (Fig. 10.10). The area of excessive bone resorption is histologically characterized by acute inflammation of the osteochondral region, thickened trabeculae of the metaphyseal bone with a thick cartilage core, necrosis, microfractures, debris, and fibrosis (Hazewinkel 1998). A similar pathological area of fractured metaphyseal bone and debris has been described in children with hypovitaminosis C (also known as scurvy). Vitamin C plays an important role in collagen biosynthesis, i.e., the hydroxylation of proline and lysine. Due to collagen fragility, blood vessel disruptions around the belly and near joints can be seen in cases of scurvy in man and guinea pigs. However, vitamin C is not an essential vitamin in dogs and cats, as demonstrated in a study in puppies raised approximately 5 months on a diet without vitamin C (NRC 2006). Due to the radiological similarities

between scurvy in children and HOD in dogs, the aetiology has long been mistaken as hypovitaminosis C in dogs and is frequently mentioned as such on the Internet and in the popular press. The lowered vitamin C content of the blood can be explained by the excessive oxidation of vitamin C in cases of a high fever, not due to a metabolic disturbance in its formation. Contrarily, high vitamin C intake has been reported to increase calcium absorption (Teare et al. 1979) and thereby increases the chance that endochondral ossification will be disturbed (Hedhammar et al. 1974; Hazewinkel, Goedegebuure et al. 1985), thus aggravating the disease. Therapy includes good nursing care during the period of the appearance of bony lesions in the metaphyseal areas (i.e., during a 3- to 4-week period), antipyretics, and analgesics. After 3 weeks, many dogs will start to walk. Caution should be used as early weight-bearing might aggravate the size of the bony cuffs, which will then not remodel completely.

PREVENTION OF NUTRITIONALLY RELATED ORTHOPEDIC DISEASES

There are three major aspects of nutritionally related orthopedic diseases that are of importance: the quality of the food, the quantity of the food, and the stage of life when the animal is vulnerable for dietary mistakes.

The quality of the food is difficult to judge, based solely on the label (see Chapter 6). Although deficient foods are uncommon, the veterinarian should be aware of the differences in dietary composition between the spectrum of products as they pertain to the various life stages and the treatment of different diseases. For example, homemade or commercially available limited antigen foods may be deficient in calcium for growth; weight-reducing diets may be rich in phytates that can bind calcium to unabsorbable complexes; diets intended solely for adult maintenance may contain dangerously high concentrations of calcium for young, fast-growing dogs (see "calcium excess" above).

The energy requirements of healthy animals vary considerably between different stages of growth (more per kg metabolic body weight during the fast growth period than later), between different breeds (smaller dogs require more energy based on their body weight; less energy is required in dogs with long hair), between different individual animals (there can be >50% difference between individual dogs), and between different activities (restrained young dogs eat less than active dogs, neutered dogs are less active). Furthermore, energy requirements can be impacted by husbandry practices such as the method of feeding (many dogs eat more when the food is provided *ad libitum*), and housing conditions (less energy is required in a warm than in a cold environment) (Gross et al. 2000). Figure 10.11 shows that the manufacturer's feeding guidelines do not take into account all of these variables; they are based on the average dog in the average household.

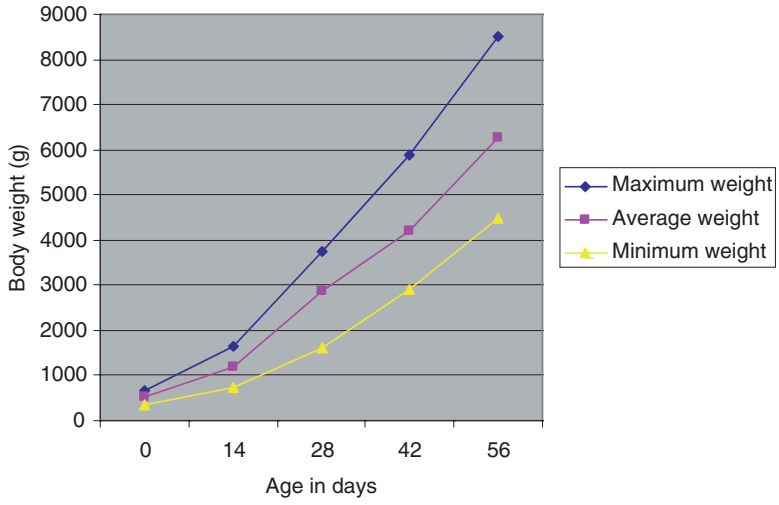


Fig. 10.11. Growth chart of German Shepherd dogs based on information from 23 breeders for a total of 442 German Shepherd puppies, revealing the most heavy, the most light, and the average weight. This figure illustrates the variation in body-weight gain and daily requirements.

Since the driving force behind food intake is the animal's energy requirement, the ratio of the ingredients to the energy content of the food is of great importance; this is especially true in minerals that will be absorbed and not excreted or metabolized, like calcium (Tryfonidou, van den Broek et al. 2002). Little is known about the optimal amount of training and playing for young dogs with a developing skeleton; it should be realized that excessive activity demands extra food intake, which includes extra mineral intake. For the former there may be a need, but not necessarily for the latter.

The influence of nutrition during different stages of development can well be illustrated by a summary of the results of a study performed in Great Danes fed a diet with 3.3% calcium and compared with Great Danes fed a control diet with 1.1% calcium (DM). Fed to pregnant bitches, this had no consequence for her or the skeletal development of her offspring. When fed to dogs only during partial weaning (3–6 weeks of age) it leads to decreased osteoclast activity (panosteitis) 3 months later, when fed from 3- to 17-week-old pups it caused hypophosphatemic rickets, and when fed from 6–21 weeks it caused severe osteochondrosis. Miniature Poodles on the same diet did not develop clinical signs of any skeletal disease (Hazewinkel, Schoenmakers et al. 1999; Nap, Mol et al. 1993). Increased calcium intake can start already at weaning, when pups are superfluously fed with artificial milk, with possibly effects at older age due to calcitonin producing C-cell hypertrophy (Corbee et al. 2011; Schoenmakers et al. 2000).

Taken together, the author recommends the following: restricted feeding of a puppy food with a calcium and vitamin D content not to exceed the percentages demonstrated in controlled studies to result in skeletal problems (i.e., calcium ~1.0% on a dry matter basis, vitamin D content 12.5–25 ug/kg diet), maintaining an optimal body condition during growth, and activity adapted to the vulnerability of the skeleton. This leaves the genetic aspect of many developmental diseases in companion animals to the responsibility of breeders.

DIETS TO SUPPORT TREATMENT OF PATIENTS WITH OSTEOARTHROSIS

Cartilage contains chondroblasts, proteoglycans, and collagen. Proteoglycans are built from glycosaminoglycans (GAGs) and a core protein called aggrecan. Aggrecan is an important proteoglycan in joint cartilage with keratin sulphate and chondroitin sulphate as GAGs. About 200 aggrecan molecules are bound via a glycoprotein to a hyaluran molecule, binding a large quantity of extracellular water, determining the compressibility of cartilage. Collagen molecules in cartilage contain large amounts of hydroxyl proline and hydroxyl lysine. The molecules form a triple helix structure, bound to fibrils and these to fibers that form a labyrinth that holds proteoglycans in place. During aging, the length of the GAGs decrease, the proteoglycan content decreases, and thus the water content and the flexibility to withstand loading also declines. Moreover, reactive oxygen species (ROS), free radicals formed during different metabolic processes, trauma, infection, and irradiation may damage GAGs.

Regeneration can occur in cases of microtrauma, by proliferation of undamaged chondrocytes, and *de novo* synthesis of proteoglycans and collagen. Severe cellular damage will lead to scarring; fibrotic cartilage scars without cells and a low content of proteoglycans.

Under normal circumstances proteolytic enzymes, mainly matrix metalloproteinases (MMPs) will be suppressed by "tissue inhibitors of MMPs," i.e., TIMPs, but in cases of OA, MMPs will be formed by mast cells and synovial cells under the influence of the cytokine interleukin-I (IL-I) and tumor necrosis factor-α, released by synovial cells, monocytes, macrophages, and T-cells. These cytokines also stimulate chondrocytes and osteoclasts to produce MMPs as soon as their surrounding cartilage has been destroyed. In addition, IL-I stimulates the release of arachidonic acid metabolites including prostaglandin from chondrocytes and synovial membrane PGE_2 and leukotriene B_4 (LTB_4) (Hazewinkel and Mott 2006) (Fig. 10.12).

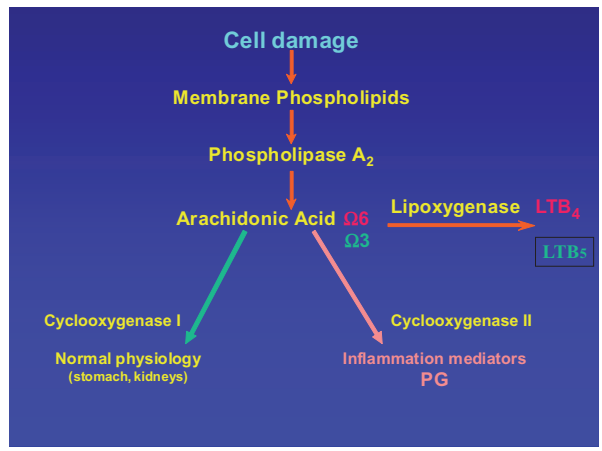


Fig. 10.12. Origin of inflammatory mediators in the joint. PG = prostaglandin; LTB4 = pro-inflammatory leukotriene B4; LTB5 = anti-inflammatory leukotriene B5.

Causative Role of Nutrition

The causes of osteoarthritis (OA) can be divided into primary OA (this is without any other cause other than aging) and secondary OA (which has a primary cause such as disturbances in development, trauma, and septic or non-septic osteoarthritis). The occurrence of primary OA may depend on the breed, i.e., the mean age of dogs varies by breed, ranging from 3.5 years in Rottweilers to 9.3 years in Miniature Poodles (Patronek et al. 1997).

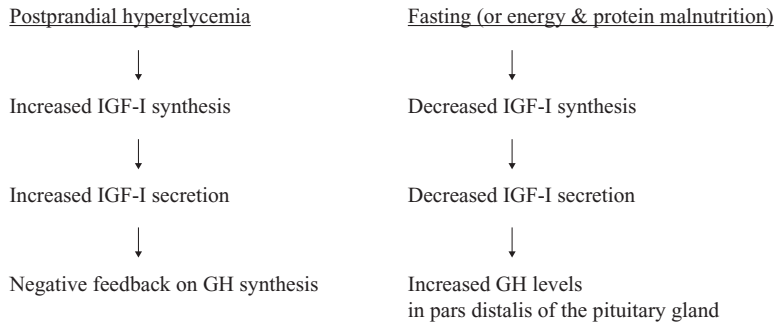
Many orthopedic developmental diseases have a low chi-square as in elbow dysplasia (chi-square = 0.4–0.7), leaving a large influence from the environment. OCD is seen more frequently in certain breeds and subpopulations and can be aggravated by high energy intake and excessive calcium intake (Hazewinkel, Goedegebuure et al. 1985) as well as by oversupplementation of balanced foods with vitamin D (Tryfonidou, van den Broek et al. 2002). Rations rich in protein do not have a disturbing influence on skeletal development (Nap, Mol et al. 1993). Great Danes raised on diets with an increased calcium and phosphorus intake (3.3% Ca and 3.0% P vs. controls on 1.1% Ca and 0.9% P, all DM) but with the same Ca:P ratio developed disturbances in endochondral ossification in the growth plates of the distal radius or ulna. As a consequence, elbow incongruity developed either due to a severe disturbance of growth in the length of the radius or due to a severe radius curvus syndrome with disturbed growth in the length of the ulna (Hazewinkel, Goedegebuure et al. 1985; Schoenmakers et al. 1999). In a study in Labradors it has been shown that OA in multiple joints (including hips, elbows, and shoulders) was seen in overweight dogs and less frequently in slim littermates (Kealy, Olsson et al. 1992; Huck et al. 2009). The frequency and severity of the occurrence of osteochondrosis can thus be decreased by dietary management, including feeding a diet with appropriate calcium-to-energy ratio, a quantitative restriction of food intake, and by not adding vitamin D to a balanced diet.

It is plausible to imagine that the specific activity of the dog may advance degeneration of joint cartilage by overuse. Overloading of the joint, either due to overuse or to overweightedness or obesity, is the main cause for increased complaints in dogs with OA. Increased energy intake (Hedhammar et al. 1974; Lavelle 1989; Kasström 1975; Kealy, Olsson et al. 1992), and increased calcium intake (Hazewinkel, Goedegebuure et al. 1985; Schoenmakers et al. 1999) may increase the frequency and severity of OA at maturity. This is nicely illustrated by the study performed by Kealy and coworkers: In two groups of Labradors, litter mates of the same gender were pair fed, i.e., one group *ad libitum*, the other two-thirds that amount (Kealy et al. 2000). Housing, food, and maintenance were the same, except for the amount of energy, and as a consequence the body weights were different between the groups. The average body weight was 32 kg for the dogs fed *ad libitum* and 23 kg for the restricted-fed dogs. At 5 years of age, 12 out of 23 *ad libitum* and 3 out of 23 restricted-fed dogs had OA of the hip joints; at 8 years, 12 of the 23 dogs fed *ad libitum* and 2 of the restricted-fed dogs had OA in multiple joints (Smith et al. 2006). The pathophysiological explanation for how obesity can induce OA has recently be reviewed (Marshall et al. 2009). It has been demonstrated that in overweight Labradors (i.e., 32 vs. 23 kg) the plasma concentration of IGF-I was significantly increased and the plasma concentration of GH was significantly decreased (Hazewinkel, Kealy et al. 1999) (Fig. 10.13).

Therapeutic Role of Nutrition

Nonsurgical therapy includes weight loss and medication. A significant improvement was recorded by Impellizeri et al. (2000) in dogs with HD, following a decrease in body weight by 11–18%. This clinical finding was supported quantitatively by force plate analysis by Burkholder et al. (2000). Adaptation to the amount and the kind of activity that does the least possible harm to the joint, preferably hydrotherapy (swimming), should coincide with a weight reduction program (Mlacnik et al. 2006). Marshall et al. (2010) demonstrated in a prospective study in 14 obese (i.e., 20% overweight) dogs that a weight reduction program improved locomotion (measured on a visual analog scale) when weight loss was 6% or more, and resulted in a better locomotion measured with force plate analysis when weight loss was 8.8% or more. This demonstrates that dogs can reveal improvement even before they reach their optimal body weight, not only due to reduced biomechanical overloading, but possibly also due to reduction of the pro-inflammatory adipokines release.

Corticosteroids suppress phospholipase activity, and consequently stabilize the blood vessel walls and the lysosomes. Joints will be less painful and less synovia is produced. Since regeneration of cartilage will be decreased under the influence of corticosteroids, long-lasting or repetitive use of corticosteroids, especially intra-articular and at higher dosages, is contraindicated. Nonsteroidal anti-inflammatory drugs (NSAIDs) have actions against cyclooxygenase (COX) enzymes; COX1 stimulates the production of prostaglandins (PGs) that protect the body, whereas COX2 stimulates the production of PGE_2, which is responsible for clinical signs like pain and hyperaemia. The latter results in warm joints and the overproduction of



It has recently become clear that adipose tissue is not only a storage form of excess calories but is also an important source of inflammatory adipokines, including leptin, IL-1, IL-6, and TNF-alpha. Leptin activates hypothalamic receptors and thus regulates appetite, but also has pro-inflammatory activity. In addition, IL-1 and TNF-alpha are produced by activated synoviocytes, mononuclear cells, and articular cartilage, and can upregulate matrix metalloproteinase gene expression involved in cartilage breakdown. Levels of these adipokines are elevated in joints affected by OA, and these adipokines can induce catabolic processes in chondrocytes, leading to cartilage matrix degradation (Griffin et al. 2011).

Fig. 10.13. Excessive food intake or fasting may influence GH and IGF-I plasma levels.

joint fluid. Selective COX2 inhibitors, with or without suppressive action on lipoxygenase, are available for dogs and claim to have fewer side effects than COX1 and COX2 inhibitors. NSAIDs, with a low incidence of side effects, should be prescribed for a prolonged period, not to mask pain but to improve the metabolic condition of the diseased joint.

To support regeneration of joint cartilage and to shorten or lower the dosage of NSAIDs there is a constant search for nutritional support for patients with OA. The term "nutraceutical" has been introduced, combining the terms "nutrition" and "pharmaceutical," and includes foods, dietary supplements, and foods that have a benefit in reducing the risk of developing a disease or managing it once it occurs (Bauer 2005). Nutraceuticals can be incorporated into functional foods or pharmaceutical preparations and do not fall under the legal categories of foods or drugs (see Chapter 5), but are included in the area between these two. The development of food components that provide benefits beyond their traditional nutritional value has great interest in several sectors: commercial, public, academic, and regulatory. The challenges relate to quality, safety, and efficacy. Most patients' owners who use nutraceuticals are of the opinion that natural remedies with a long history of use are safe, whereas neither clinical efficacy nor quality or side effects are of concern. Nutraceuticals, whether for human or veterinary use, need more pre-clinical and clinical research to evaluate the mechanisms of action, safety aspects, and efficacy, thereby allowing the veterinarian to make evidence-based decisions regarding prescription or advice of their use. These supplements, or disease-modifying osteoarthritis agents (DMOAs), include chondroitin sulphate, glucosamine, polyunsaturated fatty acids, and antioxidants (Hazewinkel and Mott 2006).

Chondroitin sulfate increases, *in vitro*, the production of proteoglycans and as such the regeneration of cartilage (Bassleer et al. 1998). It prevents synthesis of MMPs by IL-3 and thus cartilage damage when given prophylactically in rabbits.

Glucosamine is a precursor of GAGs that stimulates the synthesis of GAGs, prostaglandins, and collagen by chondrocytes *in vitro* (Bassleer et al. 1998). In cases of substitution of glucosamines in the medium of chondrocytes, the mRNA content for aggrecan is increased, MMPs decreased, and synthesis of proteoglycan increased (Henrotin et al. 2005). In rabbits with a cranial cruciate ligament (CCL) rupture, 120 mg/kg body weight of prophylactic glucosamine decreased the amount of chondropathy in comparison with controls (Conrozier 1998). In a study in dogs with a CCL rupture as a model, it has been demonstrated that these dogs had less cartilage swelling, less total and active metalloproteinase, and lower pathologic scores when

injected with 4 mg/kg BW glucosaminoglycan polysulphuric acid (GAGPS) twice weekly for 4 to 8 weeks, starting 4 weeks after the CCL rupture (Altman et al. 1989). It is suggested by Altman et al. (1989) that GAGPS suppress proteoglycan breakdown by MMPs or by directly inhibiting MMPs in cartilage, rather than by increasing synthesis of proteoglycans by chondrocytes. De Haan et al. (1994) demonstrated in a clinical, double-blind, placebo controlled trial that in dogs with hip dysplasia 4.4 mg/kg GAGPS administered intramuscular (i.m.) every 3 to 5 days improved lameness scores, range of motion, and joint pain, and had no side effects after eight injections. The placebo group of dogs only demonstrated a small improvement.

Combinations of chondroitin sulfate and glucosamine given to dogs with OA subjectively allowed for more normal locomotion and joint movement than untreated controls (Hulse 1998). Prophylactically provided, this combination decreased inflammation in dogs with induced arthritis (Canapp et al. 1999), possibly due to a modulation in the metabolism of the articular cartilage. The latter was suggested to take place in dogs with CCL ruptures, supplemented with a mixture of chondroitin sulfate, glucosamine hydrochloride, and manganese ascorbate (Johnson et al. 2001).

Polyunsaturated free fatty acids (PUFAs) have a potentially beneficial role in immunorelated disorders and OA (Bauer 1994). *In vitro* studies in canine cartilage indicated that only cartilage exposed to eicosapentanoic acid (EPA) revealed abrogating of cartilage degradation (Caterson et al. 2005). Leukotrines are formed from arachidonic acid (AA; 20:4n-6) and eicosapentanoic acid (EPA; 20:6n-3) originating from cellular membranes, under the influence of the enzyme 5-lipogenase. Proinflammatory LTB_4 originates from AA, antiinflammatory LTB_5 from EPA. The amount and type of these eicosanoids are determined by the availability of the PUFA precursor. A higher omega-3 intake results in decreased membrane AA levels and thus a decreased synthesis of eicosanoids from AA and an increase in eicosanoids derived from EPA. In joints with OA, the LTB_4 content is increased (Herlin et al. 1990). In 36 dogs with elbow OA due to ED, a double-blind efficacy study was performed by feeding an increased omega-3 content (omega-3 of 4% and omega-6 of 20%) vs. a high omega-6 content (omega-3 of 0.8% and omega-6 of 38%). The dogs that consumed the high concentrations of omega-3 fatty acids had significant increases in plasma LTB_5 concentrations, although lameness scored by ground reaction force analysis did not differ between both groups of dogs (Hazewinkel, Theyse et al. 1998).

In a clinical trial including force plate analysis performed in two groups of dogs fed either a control food or an EPA-supplemented diet for a 90-day period revealed that 31% of the controls and 82% of the EPA-supplemented group improved their weight bearing (Schoenherr 2005).

Antioxidants may decrease the damage to synovial cells by reducing ROS. For this purpose, vitamins A, C, and E, and β-carotene content in the diet can be increased.

Combinations of chondroitin sulfate, glucosamine, and polyunsaturated fatty acids are present in green-lipped mussel (GLM). The flesh part of the GLM will contain saturated, monounsaturated, and polyunsaturated fatty acids. Of the latter, a large amount is omega-3 fatty acid, mainly EPA and docosahexaenoic acid (DHA), with a final ratio of omega-6 : omega-3 = 1 : 10. GLM is claimed to be a 5-lipoxygenase-pathway inhibitor. Freeze-dried GLM powder also contains a variety of nutrients that may have a beneficial effect on joint health, including amino acids (glutamine, methionine), vitamins (E, C), and minerals (zinc, copper, manganese). The combination of omega-3 PUFAs and other ingredients may have the synergistic potential to limit the progression of OA. In a double-blind, randomized, controlled trial, 17 dogs were given a GLM supplement powder and 15 dogs a GLM supplement oil (both in a daily dosage of 1,000 mg when body weight (BW) >34 kg; 750 mg when BW was between 34 and 25 kg; 450 mg when BW <25 kg) and compared with 15 controls, all with OA. A nonobjective score of arthritic signs ranging from no clinical signs to severe clinical signs was given for mobility and for all major joints individually, before the start of the study and at 6 weeks. Joint swelling, pain, and crepitus were reported to improve in the GLM-powder supplemented group in comparison with the controls; the GLM-supplemented group was only significantly different in joint pain and crepitus scores (Bierer and Bui 2002). All three dosages resulted in a similar improvement in total arthritic score and all significantly different from controls. However, no significant effects were observed with regard to mobility and reduction in range of joint movement with the addition of GLM in any of the studies. Longer studies and more sensitive assessment methods may be helpful in detecting any possible effects in these parameters (Bierer and Bui 2002).

There is great interest in the discovery of natural products to be used as DMOAs, based on the aversion to "chemical substances" (i.e., NSAIDs) that exists among many dog owners. This interest, as well as the laxity in efficacy control, dosage, and purity makes them easy to

incorporate into dog food. There is a growing need for double-blind clinical efficacy studies with objective criteria to support the *in vitro* evidence that these DMOAs, nutraceuticals, and supplements may be beneficial to patients suffering from OA. Meta-analyses of the efficacy of glucosamine and chondroitin sulfate for treatment of OA in man led to different conclusions; the ingestion of glucosamine or chondroitin sulfate demonstrated some efficacy in some symptom-relieving parameters, but the ability to modify the structure of articular cartilage was not confirmed (Table 10.8) (McAlindon et al. 2000). At the level these substances are included in most pet foods there is scarcely research available to demonstrate a direct therapeutic effect to support their use in the treatment of OA in dogs (Schoenherr 2005). Claims for different concentrations or combinations of nutraceuticals, the period when efficacy can be expected, the use in particular breeds or sizes of dogs, and the indication for different joints or stages of OA will keep the scientific world busy until the onus of proof is laid in the hands of those who claim the efficacy.

Other supplements are under study (Curtis et al. 2004) including green tea and herbal extracts. As can be seen from the findings above, providing preliminary information should be considered with care. Results should be gathered in the target species (i.e., the dog) and not in small laboratory animals, in man, or in *in vitro* studies. The dosage, duration, and route of the DMOAs should be taken into account. Since most of these products are not pharmaceuticals, neither purity nor content is, per se, under strict control, even though the package or information material may suggest otherwise. The daily intake, together with the food, can have practical advantages, i.e., client compliance is greater, and the supplement will get its chance for long-term effects. However, parenteral application has its advantage to overcome biological unavailability, used only when (still) indicated or stopped and replaced by other prescriptions or modalities when not effective.

Double-blind studies are a necessity, and the use of objective measures (e.g., force plate, determination of relevant markers) make multicentric trials possible to learn more about the efficacy of these and future nutraceuticals.

The varying responses in these and other trials have been suggested to be due to the lack of stabilizing processes, avoidance of heat during the processing of the diets, the ratio of omega-3 to omega-6 FA (i.e., the effect

Table 10.8. Nutraceuticals and Claimed Effects on Joints With Osteoarthritis

Supplement	Function	Effect on Joints	Oral Dose in Dogs
Glucosamine[1]	Precursor of GAG	Limit or delay OA in senior patients	0.02 mg/kg
Chondroitin Sulfate[2]	a GAG	Stimulates GAG synthesis, inhibits degradative enzyme action	25 mg/kg
Polysulfated GAG[3]		Analgesic, anti-inflammatory, chondroprotective	5 mg/kg
Omega-3 fatty acids[4]	Precursor of EPA and DHA	Anti-inflammatory	
Vit E[5]	Antioxidants	Minimize damage from free radicals	Vit E 2.5 mg/kg
Green-lipped mussel[6]	FA 3 : 6 = 1 : 10 (EPA & DHA) chondroitin, (6.9%), glutamine (0.0005%), and antioxidants	Anti-inflammatory, blocking COX and lipoxygenase pathway	Body weight >34 kg: 1,000 mg; 34–25 kg: 750 mg; <25 kg: 450 mg

[1]Setnikar et al. 1991.
[2]Usually given in combination with other chondroprotective agents.
[3]Setnikar et al. 1991; De Haan et al. 1994; Altman et al. 1989.
[4]Bauer 1994.
[5]Greenwald 1991; Kurz et al. 2002.
[6]Bierer and Bui 2002.

of the background diet), the purity and dosage of the product, and the significant placebo effect (Curtis et al. 2004; Cobb and Ernst 2006; Dobenecker et al. 2002). The strong influence of the latter by the awareness of the owner concerning the OA of their pet and the necessity of adapting the dog's lifestyle is the experience of most veterinary surgeons who evaluate therapies (Marcillin-Little 2004), but is perhaps not as high as in human studies(~60%) (Clegg et al. 2006). Dobenecker et al. (2002) described that some symptoms improved even more in the placebo group than in supplemented groups and concluded that studies in assessing the efficacy of chondroprotective agents must therefore be carried out with placebo controlled, double blinded, and preferably with objective study measures.

SUMMARY

- Nutrition plays an important role in undisturbed skeletal growth and remodeling.
- Both deficiency and excess of minerals (calcium, phosphorous) and vitamins (vitamin D and vitamin A) may be the causative factor of a variety of orthopedic diseases including pathological fractures, rickets, radius curvus syndrome, wobbler syndrome, panosteitis, osteochondrosis, incongruity of the elbow joint, and possibly other forms of elbow dysplasia and dysplasia of the hip joint.
- Large breed dogs especially should be fed according to, and not exceeding, the nutrient requirements.
- Minerals and vitamins are part of the diet, providing the energy for growth and activity. Individual variation, increased growth rate and/or level of activity may lead to exceeding the daily requirements of minerals and vitamins and thus to disturbance of skeletal growth as a cause of frequently diagnosed orthopedic diseases.
- Obesity in dogs is linked to lameness due to osteoarthritis.
- Insight in mineral and bone metabolism, the pathophysiology of orthopedic diseases related to deficient or excessive intake of food constituents will help to understand and thus to prevent these diseases and to educate the clients accordingly.

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Nutritional Management of Skin Diseases

11

Catherine A. Outerbridge

The skin can provide cues and clues to underlying systemic health. The appearance of the skin and hair coat is influenced by the nutritional intake of an animal. The skin can develop lesions secondary to nutritional deficiencies; however, this is very uncommon in a healthy animal that has a good appetite and is being fed adequate amounts of an appropriate food. A number of skin diseases are managed with nutritional alterations in the actual dietary ingredients fed to the animal or the addition of supraphysiologic supplementation of certain dietary elements. This chapter will discuss those dermatologic diseases or conditions that are the result of nutritional deficiencies or managed by changes in diet or nutritional supplements.

NUTRITIONAL DEFICIENCIES

Nutrients that can result in cutaneous manifestations, should marked deficiencies occur, include protein, essential fatty acids, zinc, copper, vitamin A, vitamin B complex, and vitamin E as in table 11.1. Dermatologic conditions associated with nutritional deficiencies are uncommon if the animal is being fed a diet that meets the nutritional needs for that individual. Some cutaneous manifestations of nutritional deficiencies in dogs are recognized in particular breeds, suggesting perhaps an alteration in absorption or metabolism within those individuals, while others have been linked to inadequate or unbalanced diets.

Protein

Protein deficiency can occur and affect the skin if an animal is consuming a very low protein diet, experiencing a severe catabolic process, or enduring a period of starvation. Lesions are more prominent in young, growing dogs whose protein requirements are higher**.** The skin has high needs for protein and energy. Hair is 95% protein, and hair growth can utilize up to 30% of the daily protein intake (Scott et al. 2001b). Certain amino acids are particularly important for the growth or production of normal hair or skin. Hair contains large amounts of the sulfur containing amino acids, methionine, and cysteine. Cysteine can form disulfide bonds to form cystine, which is a major constituent of hair as several of the keratin-associated proteins in hair fibers contain high amounts of cystine (Shimomura et al. 2003). Tyrosine is an important precursor for the production of melanin and normal production of the eumelanin and pheomelanin found in hair (Yu et al. 2001). Animals with protein deficiency have scaling, loss of hair pigment, and patchy alopecia. Hair shafts become thinner, and the overall hair coat quality is poor with dry, dull, brittle hair shafts. In humans, a mean hair root diameter of less than 0.06 mm suggests protein deficiency but no similar specifications are available for animals (Scott et al. 2001b). These hair shaft lesions, together with scales and crusts, may appear symmetrically on the head, back, thorax, and abdomen, and on the feet and legs**.** Wound healing is delayed so that wound dehiscence and decubital ulcers are also possible cutaneous lesions of protein deficiency (Rhoads et al. 1942). Animals that are ill or have metabolic stress may suffer from anagen or telogen defluxion that may in some cases be the result of inadequate amounts of protein and energy during these periods.

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Table 11.1. Dermatologic Signs Associated With Nutritional Deficiencies

Dietary Deficiency	Skin Lesions
Protein	Scaling. Patchy alopecia. Thin brittle hair shafts. Loss of hair pigment. Decreased wound healing.
Essential Fatty Acids	Mild scaling. Lack of luster to coat. With chronicity skin thickens and becomes greasy.
Zinc	In dogs, erythema, scaling, adherent scaling and crusts develop around mucocutaneous junctions and pressure points.
Copper	Hair depigmentation and rough, dull hair coat.
Vitamin A	Scaling, follicular hyperkeratosis, dull hair coat.
Vitamin E	In cats, steatitis: firm, nodular, painful subcutaneous swellings.
Vitamin B complex	Dry hair coat with scaling: cheilosis with riboflavin deficiency.

Anagen defluxion or effluvium results in alopecia when hairs that are in the anagen stage of growth are lost or damaged. This can occur with certain metabolic disorders, endocrinopathies, and the administration of antimitotic drugs. Telogen defluxion or effluvium occurs when there is a sudden growth arrest of numerous anagen follicles and then synchronization of these follicles into telogen. Causes of telogen defluxion include severe illness, high fever, physiologic shock, surgery or anesthesia, or pregnancy. Typically over a 1- to 3-month period after the insult, the majority of hairs from these follicles are shed as a new hair follicle cycle begins.

Increasing the animal's consumption of high-quality protein sources should resolve the cutaneous signs if there is no underlying complicating disease process.

Essential Fatty Acids

Polyunsaturated fatty acids (PUFAs) are needed to maintain normal structure and function of the skin. Essential fatty acids (EFAs) are polyunsaturated fatty acids that must be acquired from the diet as the animal cannot synthesize them. Depending on the species, the EFAs include the omega-6 (n-6) fatty acids, linoleic (LA), and arachidonic (AA) acids. Cats cannot biotransform LA to AA, and thus for cats AA is also an essential fatty acid. The omega-6 fatty acid LA is derived from vegetables and seed oils (e.g., safflower, sunflower, corn). Gamma linolenic acid is another omega-6 fatty acid and is derived from seed oils of evening primrose, borage seed, or black currant that can be used to substitute for animal-derived AA. The omega-3 (n-3) PUFA alpha-linolenic acid (ALA) n-3 is not an essential fatty acid. In addition, dogs cannot effectively convert ALA to docosahexaenoic acid (DHA) (Dunbar et al. 2010), so algal/fish oils, rather than seed oils, are a better source if long-chain n-3 fatty acids are desired (Bauer et al. 2006). Other dietary sources for the omega-3 PUFA ALA include grain oils [e.g., canola or linseed (aka flaxseed)] and green leafy vegetables. Eicosapentanoic acid (EPA) is another long-chain omega-3 PUFA that is found in high amounts in marine fish oil.

EFAs have multiple functions in the skin and are involved in the synthesis of prostaglandins and leukotrienes, and they affect the fluidity of the phospholipid cell membrane (Kwochka 1993). EFAs, particularly linoleic acid (LA) are an important component of ceramides, which are necessary in maintaining the cornified lipid envelope or skin barrier. Arachadonic acid can influence epidermal proliferation via the production of prostaglandin E_2. The skin is an active lipid synthesizing and metabolizing organ with a large membrane store of AA, but the skin cannot convert LA to AA as it lacks the enzymes required to perform the necessary elongation. If LA and AA are deficient in the diet, which can occur if the diet is low in fat, the diet has been poorly preserved (i.e., exposure to high heat, use of already rancid raw material during production, or devoid of or possessing an inadequate amount of protective antioxidants), or, in rare cases, if the animal suffers from intestinal malabsorption, exocrine pancreatic disease, or chronic hepatic disease, then cutaneous signs of EFA deficiency can occur (Scott et al. 2001c; Codner and Thatcher 1993; Watson 1998).

Essential fatty acid deficiency in dogs and cats is characterized biochemically in the skin by the absence of LA and AA, and by the accumulation of the monounsaturated fatty acids oleic and mead fatty acids. When these fatty acids replace AA in cell membranes, membrane integrity is compromised, and when oleic acid replaces LA in ceramides there is increased transepidermal water loss (TEWL). The decrease in AA may also result in a decrease in prostaglandin E_2 and resultant epidermal proliferation. Clinically, in early EFA deficiency a fine scaling is observed with a loss of luster and sheen of the hair coat. Chronic EFA deficiency results in skin thickening with greasiness, particularly in the ears and intertriginous zones.

The diagnosis is confirmed by response to EFA supplementation either by feeding a better quality diet with higher fat content or administration of a veterinary fatty acid supplement. A better quality dog food is preferred as it will also meet all nutritional needs for vitamins and minerals. Response is typically rapid with improvement seen within 4 to 8 weeks.

Zinc

Zinc is an important dietary element for the development of normal epithelialization (Watson 1998). It serves as a cofactor in numerous transcription factors and enzyme systems including RNA and DNA polymerases, and it is therefore very important in tissues, such as the skin, that frequently undergo cell renewal. Zinc-dependent matrix metalloproteinases are involved in keratinocyte migration and wound healing. The skin contains approximately 20% of the total body zinc stores, and the highest concentrations of zinc are found in the keratinized tissue of the nasal planum, tongue, and footpad in dogs (Lansdown and Sampson 1997). There are a number of recognized syndromes associated with either zinc deficiency or disturbances in zinc assimilation that present with cutaneous signs.

There are two syndromes of zinc responsive dermatosis seen clinically in the dog. Syndrome I has been identified in Siberian Huskies, Alaskan Malamutes, and occasionally other breeds. These dogs are speculated to have a genetic defect in the intestinal absorption or the metabolism of zinc. In Malamutes it has been shown that a decreased capability for zinc absorption from the intestine exists in those dogs affected with chondrodysplasia (Brown et al. 1978). Skin lesions develop despite adequate consumption of diets with sufficient zinc. Syndrome II occurs in rapidly growing puppies that are often being fed a poor-quality dog food that is deficient in zinc, a cereal or soy diet with high amounts of phytates, or are oversupplemented with calcium (Watson 1998). These juvenile dogs are thought to have a relative zinc deficiency caused by a combination of low zinc intake and/or the effects of excessive calcium or phytate from the diet that interferes with zinc absorption.

Affected Syndrome I dogs typically present with crusting, scaling, and alopecia of the facial mucocutaneous junctions particularly the periocular region, perioral, and pinnal margins, but elbows, pressure points, and footpad margins can also be affected. Lesions progress from erythema followed by variable alopecia with fine silver scaling that becomes adherent or develops into crusting with underlying suppuration most commonly around the mouth, chin, eyes, and ears. Lesions are often well demarcated and unilateral initially but become symmetrical as the disease progresses (see Figs. 11.1 and 11.2). Lesions develop early in adulthood (1 to 3 years of age) and progress at a variable rate. Lesions may be pruritic in about half of affected dogs (Colombini and Dunstan 1997). Affected Syndrome II dogs are large breed, young growing dogs that have marked crusting lesions often over pressure points or on the muzzle. Footpads can be very hyperkeratotic with fissuring.

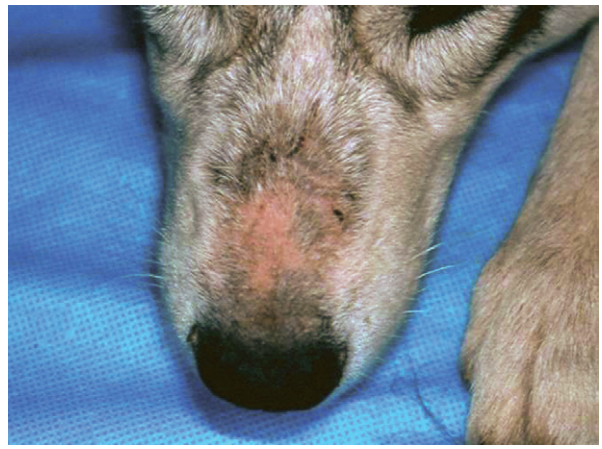


Fig. 11.1. Type 1 zinc deficiency in a Husky dog. There is adherent scale, crusts, and erythema with alopecia present over the dorsal muzzle.

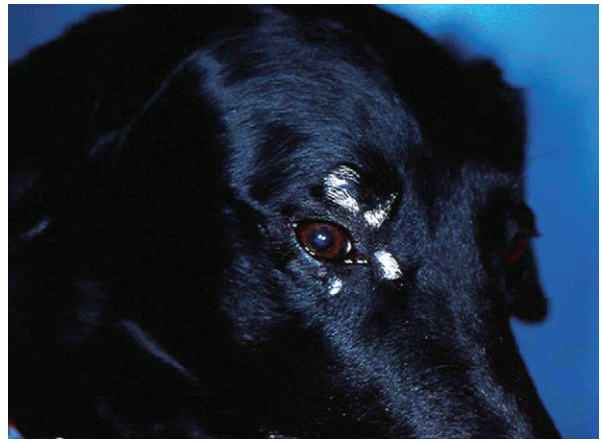


Fig. 11.2. Type 1 zinc deficiency in a non-arctic breed dog. There is a well-demarcated area of alopecia with thick adherent silver-colored scale in the periocular region.

Diagnosis of Syndrome I zinc responsive dermatosis is based on appropriate signalment, diet history, typical cutaneous lesions, and histopathology of skin biopsies. Marked follicular and epidermal parakeratotic hyperkeratosis is evident histologically. Diagnosis of Syndrome II zinc dermatosis is based on compatible signalment, diet history, and clinical signs with histopathology similar to that seen in Syndrome I. Diagnosis for both syndromes is further confirmed by response to zinc supplementation. Quantification of zinc levels in serum, plasma, leukocytes, and hair does not appear to be a reliable indicator of zinc status in dogs (van den Broek and Stafford 1988; Logas et al. 1993).

Therapy requires zinc supplementation with a recommended dosage of 2–3 mg/kg of body weight of elemental zinc in the form of zinc sulfate, zinc gluconate, or zinc methionine (White et al. 2001). Although zinc when fed as a zinc-amino acid chelate (such as zinc methionine) is thought to be more bioavailable, that may be most important when there are diet or physiologic conditions that limit zinc availability or increase the need for it (Roudebush and Wedekind 2002). To date there does not seem to be associated differences in clinical response with the different forms or salts used for zinc supplementation for dogs with Syndrome I zinc responsive dermatosis (White et al. 2001). Clinical signs are typically improved within 4 to 6 weeks. Affected female dogs often respond to lower dosages of zinc after being spayed, suggesting that zinc needs are greater during estrus or that zinc and estrogen compete for carrier proteins (White et al. 2001). In both syndromes of zinc responsive dermatosis, fasting and postprandial concentrations of serum triglycerides have been shown to be significantly lower in successfully treated dogs compared with normal dogs (van den Broek and Simpson 1992). EFA deficiency impairs zinc absorption, and supplementation with EFAs appears to enhance zinc absorption (White et al. 2001, Huang et al. 1982). EFA and zinc metabolism in rodents is closely linked; zinc deficiency accelerates the development of clinical signs of EFA deficiency and the clinical signs of zinc deficiency can be partially reversed by supplementing with EFA (Cunnane et al. 1980) Several of the manifestations of zinc deficiency are mediated by a relative state of EFA deficiency attributed in part to reduced delta-6-desaturase enzyme activity that needs zinc as a cofactor and is a critical enzyme in fatty acid metabolism**.** Low-dose corticosteriods may be indicated in some dogs that do not respond to zinc alone. Corticosteroids are known to increase metallothionein, a zinc carrier protein, and they may also have some direct anti-inflammatory effect on the skin.

Response to zinc supplementation is dramatic in Syndrome II zinc deficiency but is often not needed once the dog has reached maturity, unlike dogs with Syndrome I zinc deficiency. Many Syndrome II dogs will respond to simply feeding a better quality diet.

There has been a report of zinc responsive dermatitis in related Pharaoh Hound puppies (Campbell and Crow 2006). Dogs developed cutaneous lesions in the first months of life that histologically were suggestive of an underlying zinc deficiency. Affected puppies also had systemic signs of lethargy, poor growth, and mental dullness. Dogs did not respond to oral supplementation and intravenous supplementation with zinc sulfate was required to produce amelioration of clinical signs.

Lethal Acrodermatitis in White Bull Terriers

Lethal acrodermatitis (LAD) is an autosomally recessive disease seen only in white Bull Terriers. The homozygously affected puppies show clinical signs in the first few weeks of life and have a median survival of 7 months, typically succumbing to bronchopneumonia and sepsis. Bull Terriers that are heterozygously affected may exhibit increased risk for the development of pyoderma. A disease in humans called acrodermatitis enteropathica occurs as both a heritable disease and also an acquired form and has some similarities to both the clinical and histopathologic features of acrodermatitis in the white Bull Terriers. The heritable disease in humans has been shown to be an autosomal recessive genetic defect in a zinc transporter protein (Wang et al. 2002). Skin lesions in LAD affected dogs are characterized by a progressive crusting dermatitis of the distal extremities and mucocutaneous junctions. Abnormal keratinization of paw pads can result in splaying of the feet. Claw dystrophy and paronychia may be present. Secondary infections of the skin with bacteria and yeast are common. Dogs with LAD also often have an abnormally arched hard palate, retarded skeletal growth, abnormal mentation, diarrhea, and bronchopneumonia. In a report of 28 affected dogs, all had difficulty eating, stunted growth, splayed digits, and they had developed skin lesions by 12 weeks of age (McEwan et al. 2003). The cutaneous signs are suggestive of severe zinc deficiency. Serum zinc and copper concentrations were lower ($P < 0.05$) in dogs with LAD, compared with values for control dogs (Uchida et al. 1997); however, other studies have not found serum zinc concentrations to be a useful diagnostic tool for LAD (McEwan et al. 2003). Dogs with LAD have been shown to have significantly lower IgA levels than a control group of dogs (McEwan et al. 2003). A diagnosis of LAD can be strongly suspected in any Bull Terrier showing a

combination of the aforementioned signs from an early age. Skin biopsy reveals a marked parakeratotic hyperkeratosis. Although many of the clinical signs and the pathology of this condition suggest zinc deficiency, zinc supplementation is of little benefit and there is no effective therapy.

Generic Dog Food Dermatosis

A dermatosis associated with the exclusive feeding of a poor-quality dog food was reported in the 1980s (Sousa et al. 1988). This disease is seen less commonly in North America since the adoption of additional pet food regulations. Many of the affected dogs were typically less than a year of age and were undergoing a period of rapid growth.

The dermatosis is characterized by the presence of well-demarcated, thick, crusted plaques with fissures and erosions (see Fig. 11.3). These lesions are typically located on the muzzle, mucocutaneous junctions, over pressure points and on distal extremities. Affected dogs can also have concurrent pyrexia, malaise, dependent edema, and lymphadenopathy. A deficiency of multiple trace minerals, vitamins, EFAs, and amino acids was likely the cause of the cutaneous lesions. Diagnosis is based on a compatible diet history and histopathologic evaluation of skin biopsies. Histopathology of representative skin lesions reveals a markedly acanthotic epidermis with parakeratosis, crusting and spongiosis. Lesions resolve with feeding a better-quality diet.

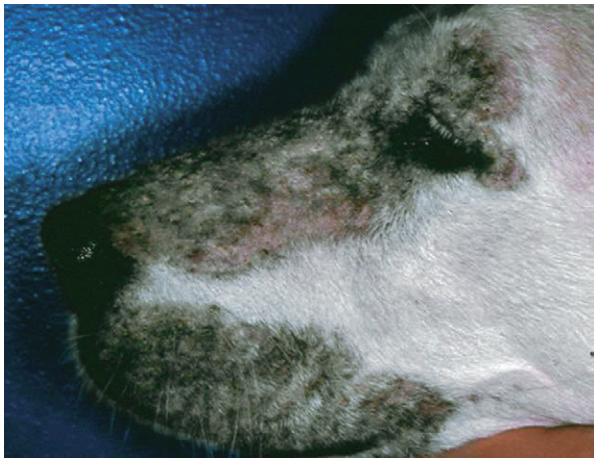


Fig. 11.3. Generic dog food disease in a young Labrador. There are areas of well-demarcated crusted plaques with erythematous borders periorally and periocularly.

Copper

Copper is required for melanin production and keratin synthesis. Copper deficiency is unlikely, as commercial diets contain adequate copper but supplementation with other minerals such as zinc or calcium could cause imbalances. Cutaneous lesions seen with copper deficiency include hypopigmentation with a dull rough haircoat (Scott et al. 2001d). White Bull Terriers with LAD have been shown to be copper deficient (Uchida et al. 1997).

Vitamin A

Vitamin A has an important role in the health of the skin. Vitamin A and retinoids influence cell proliferation and differentiation of keratinizing epithelium. Both vitamin A deficiency or hypervitaminosis A can cause skin lesions that manifest as scaling, poor hair coat, alopecia, and an increased tendency for pyoderma (Scott et al. 2001d; Watson 1998). There is only one report of true vitamin A deficiency in a dog that had severe seborrheic skin lesions with hyperpigmentation and alopecia (Scott et al. 2001d).

Vitamin A responsive dermatosis is a rare skin disease seen predominantly in Cocker Spaniels (Ihrke and Goldsmith 1983). It is an adult onset cornification disorder in which dogs present with multifocal, well-demarcated, erythematous, alopecia plaques with thick adherent scale most often located on the ventral abdomen and thorax. Hair shafts are often entrapped and clumped by keratinaceous debris. Overall the hair coat is dull. Histologically, severe follicular hyperkeratosis is evident and this is highly suggestive for the diagnosis (Gross et al. 2005). Despite being fed a nutritionally balanced diet, these dogs require supraphysiologic supplementation with oral vitamin A at 600 to 800 IU/kg of body weight/day. Clinical improvement is typically seen in 6 to 8 weeks. Some degree of lifelong supplementation with vitamin A is often needed. High doses of vitamin A are likely to have some degree of a suppressive effect on cornification in these dogs and slow the epidermal turnover time.

Vitamin E

Vitamin E is an antioxidant and is important in maintaining stability of cell membranes. Working with glutathione peroxidase and selenium, vitamin E is capable of protecting cells against the adverse effects of reactive oxygen and other free radicals that initiate the oxidation of polyunsaturated membrane phospholipids.

Pansteatitis is associated with diets that are low in vitamin E and high in polyunsaturated fats. A diet comprised entirely of raw oily fish is a classic example. Cats with pansteatitis develop firm painful swellings associated

with the inguinal and abdominal fat pads. The swellings result from the inflammation associated with the peroxidative damage of adipose tissue. Cats may be painful and reluctant to move, anorexic, or febrile. It is important to differentiate this disease from panniculitis caused by infectious agents such as the opportunistic mycobacteria that can often cause nodular lesions on the ventral abdomen. Diagnosis is made based on a diet history and histologic evidence of steatitis on biopsy. Biopsy reveals lobular panniculitis with macrophages and giant cells, and there is ceroid within lipocytes. Correcting the dietary deficiency with vitamin E supplementation will improve clinical signs.

Experimentally induced vitamin E deficiency has been reported in dogs to cause a cornification disturbance that is initially a dry scaling that becomes more inflamed with erythema, skin thickening and increased greasiness (Scott and Sheffy 1987). Cutaneous signs resolved within 10 weeks of feeding a diet with adequate vitamin E supplementation.

Vitamin B Complex

The B vitamins are water soluble and are involved as cofactors in a number of metabolic pathways. Deficiencies can occur if animals have enteritis, exhibit polyuria, or have been receiving prolonged courses of antibiotics. The most common clinical skin change seen with deficiencies of the B vitamin complex is a dry scaling with alopecia. Clinical signs associated with individual B vitamin deficiencies have been described but are rare.

Biotin deficiency can result in facial and periocular alopecia in dogs that can progress to more generalized crusting lesions (Scott et al. 2001d; Watson 1998). In the cat, generalized dermatitis with crusted papules has been described (Scott et al. 2001d). Biotin deficiency can occur if the diet contains high amounts of uncooked egg whites, which contain avidin, which binds biotin.

Riboflavin deficiency can cause a dry, scaling dermatitis around the eyes and the ventrum and a marked cheilosis in dogs (Lewis et al. 1987). However, riboflavin deficiency is unlikely if the diet contains any meat or dairy products.

Niacin deficiency results in pellagra, which is characterized by ulcerated mucous membranes, diarrhea, emaciation, and in some dogs, pruritic dermatitis of the ventral abdomen and hind legs (Scott et al. 2001d). Niacin deficiency is possible if a diet low in animal protein and high in corn is fed. Corn is low in tryptophan, which is required for niacin synthesis in dogs.

Pyridoxine deficiency has only been seen in an experimental setting in cats. The cats developed a dull, waxy, hair coat with generalized scaling and focal alopecia involving the face and extremities (Norton 1987; Scott et al. 2001d).

SKIN DISEASES THAT BENEFIT FROM NUTRITIONAL OR DIETARY MANAGEMENT

The next section will discuss dermatologic diseases for which dietary modifications are paramount for the management of the skin disease.

Superficial Necrolytic Dermatitis

Hepatocutaneous syndrome (HCS) is an uncommon skin disorder associated with systemic metabolic disease. It has also been called superficial necrolytic dermatitis (SND), metabolic epidermal necrosis (MEN), diabetic dermatopathy, and necrolytic migratory erythema (NME). The first English language reference comparing it to the human disease NME was in 1986 when the HCS was described in four dogs with diabetes mellitus and therefore called diabetic dermatopathy (Walton et al. 1986). As different disease processes appear to cause similar histologic skin lesions, it might be more accurate to refer to the skin disease as either SND or MEN. The disease has been most commonly described in older dogs, although there are reports of a histologically equivalent disease that occurs in cats and the black rhinoceros (Patel et al. 1996; Day 1997; Munson et al. 1998). The etiopathogenesis of this disease is unclear but it is likely multifactorial.

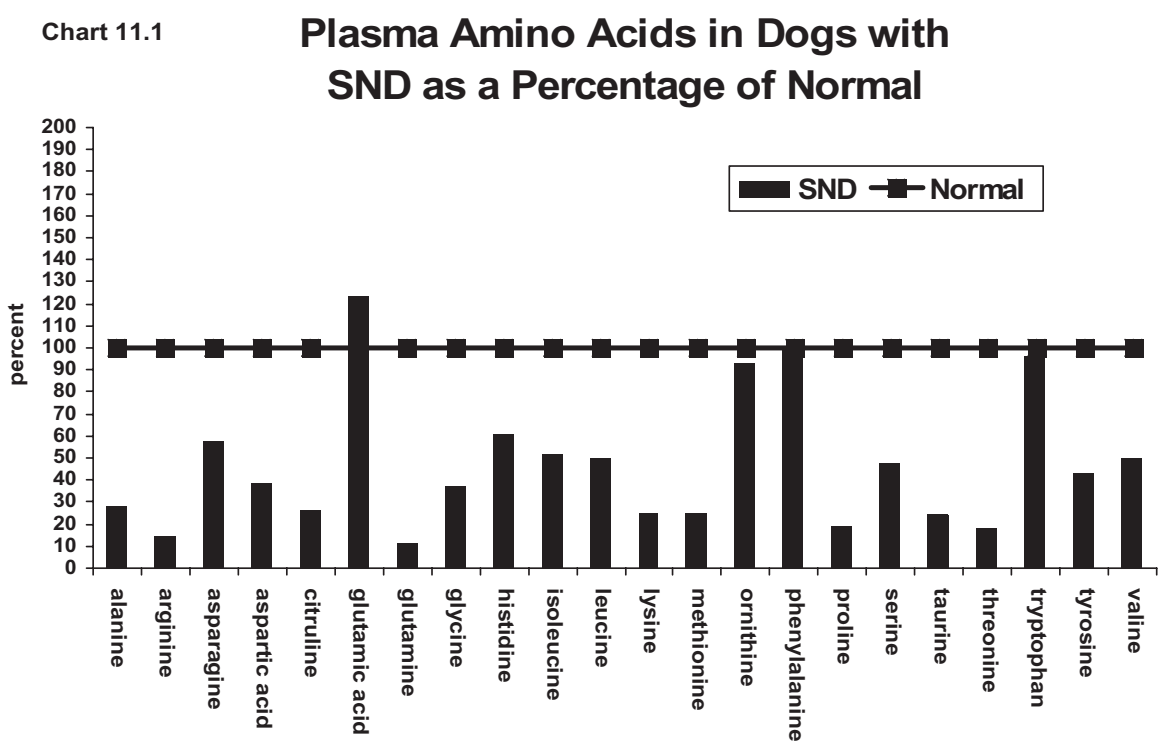
Necrolytic migratory erythema (NME) is a histologically similar disease that is seen in humans. Most often, NME occurs in association with a glucagon-secreting tumor. Unlike people with NME, association with glucagonoma has not been consistently demonstrated in the majority of dogs with the skin lesions of SND. Afflicted dogs commonly have a characteristic concurrent hepatopathy, thus the use of the term “hepatocutaneous syndrome” (HCS). The hepatic pathology seen in dogs with HCS has not been reported to occur in those dogs with confirmed glucagonoma-associated SND. In addition to the association with hepatic pathology, there are dogs with the skin lesions of SND that have a history of phenobarbitol administration (Bloom et al. 1992; Byrne 1999; March et al. 2004), and some with gastrointestinal signs and malabsorption (Florant et al. 2000).

The severe vacuolar liver disease seen in the majority of dogs with the skin lesions of SND and the association in some dogs with concurrent diabetes mellitus suggests that an underlying hormonal or metabolic disturbance is occurring in dogs with HCS. Diabetes mellitus has been reported to occur in 25% to 40% of dogs with HCS (Byrne 1999; Outerbridge et al. 2002). Hypoaminoacidemia has

been documented to occur in all reported dogs with SND skin lesions that have, thus far, had concentrations of plasma amino acids measured. Most dogs had non-glucagonoma-associated disease or HCS, and only three dogs for which plasma amino acids were measured were confirmed to have a pancreatic tumor (Bond et al. 1995; Torres et al. 1997; Allenspach et al. 2000). The pattern of the plasma amino acid panels in dogs with SND appears to be significantly different from that seen in dogs with acute or chronic hepatitis.

The liver plays a critical role in amino acid balance. In both chronic and acute hepatitis the compromised hepatic metabolism results in increased concentrations of many plasma amino acids. However, this is not seen in dogs with SND, as the majority of individual plasma amino acid concentrations are less than 60% of normal (see Chart 11.1). Total amino acid concentrations documented in dogs with SND are approximately 30% of the concentrations documented in healthy dogs or dogs with acute or chronic hepatitis (Outerbridge et al. 2002). These differences suggest that the pathogenesis of hypoaminoacidemia in dogs with SND cannot be explained by compromised hepatic metabolism. The ratio of branch chain amino acids (BCAA) to aromatic amino acids (AAA) has been recognized as an indicator of hepatic insufficiency, and this ratio decreases with the severity of hepatic dysfunction or portal-systemic shunting. The mean BCAA:AAA ratio in dogs with SND in one study was 2.6 : 1.0, which is not indicative of severe hepatic dysfunction (Outerbridge et al. 2002). It seems probable that an as yet unexplained increase in hepatic catabolism of amino acids might account for the severity of the hypoaminoacidemia documented in the dogs with SND. Intravenous administration of amino acids initially bypasses the portal circulation resulting in the delivery of amino acids to peripheral tissues before hepatic uptake and catabolism can occur. The fact that some dogs respond better to therapy with intravenous amino acid infusions rather than oral protein hyperalimentation supports the hypothesis that there is increased hepatic catabolism of amino acids in dogs with SND.

Chart 11.1



Plasma amino acids in dogs with SND as a percentage of normal. The majority of individual plasma amino acid concentrations in dogs with SND are less than 60% of normal. Plasma amino acid concentrations in 36 dogs with histologically confirmed superficial necrolytic dermatitis (SND) (Outerbridge et al. 2002).

The etiopathogenesis of the hepatic pathology seen in the majority of dogs with SND remains unknown, and it is unclear what metabolic pathways may link liver or pancreatic disease with the skin lesions seen in SND. Hyperglucagonemia, if it were present, could explain the risk for the development of diabetes mellitus and hypoaminoacidemia seen in dogs with SND. Glucagon is not a hormone routinely measured in dogs and assays may not detect all biologically active metabolites of glucagon. The catabolism of almost all amino acids is influenced by glucagon except tryptophan (Shepartz 1973). Tryptophan concentrations are not significantly decreased in dogs with SND (Outerbridge et al. 2002). It is possible that a disturbance in glucagon metabolism may have a role in the HCS form of SND. Adding to the confusion about the pathogenesis of this disease is the fact that dogs with histologically confirmed glucagonomas do not seem to have the same hepatic pathology as seen in dogs with HCS.

The actual etiopathogenesis for the skin lesions seen in dogs with SND or in humans with NME is not known. Humans with NME have had resolution of their lesions after surgical excision of their glucagonoma or after the use of somatostatin analogs (Sohier et al. 1980). This suggests that hyperglucagonemia may have a direct role in the development of the skin lesions. It has been suggested that in NME, hyperglucagonemia results in increased epidermal arachidonic acid and the resultant metabolites are responsible for the inflammatory changes in the skin (Peterson et al. 1984). However, evidence exists that glucagon alone cannot explain the development of NME lesions in all affected humans, as some have had resolution of skin lesions despite persistent increased glucagon concentrations (Sohier et al. 1980; Mullans and Cohen 1998). Some patients with nonresectable pancreatic tumors have had NME skin lesions resolve with administration of intravenous amino acids (Marinkovich et al. 1995; Mullans and Cohen 1998). This finding, along with the hypoaminoacidemia seen in the majority of glucagonoma NME patients, has led to the hypothesis that increased gluconeogenesis triggered by hyperglucagonemia results in low plasma amino acid concentrations, epidermal protein depletion, and then the skin lesions of NME. Hypoaminoacidemia was proven to result from increased hepatic clearance in one human patient with a glucagonoma (Almdal et al. 1990). Essential fatty acid and zinc deficiencies have both been proposed to contribute to the development of NME because the histologic appearance of skin lesions in patients with zinc deficiency (acrodermatitis enteropathica) or EFA deficiency shares some similarities to that seen in NME. Some patients have had improvement of their NME skin lesions after zinc or EFA supplementation, but neither has proven to be helpful for long-term resolution of the skin lesions in NME in human patients or HCS in dogs (Kasper 1992).

In dogs with SND associated with glucagonoma, pancreatic tumor excision or treatment with somatostatin has resolved skin lesions (Torres et al. 1997; Oberkirchner 2009). As different disease processes appear to be able to produce the same characteristic histologic skin lesion, this suggests that perhaps they may be all due to a common metabolic disturbance. The fact that severe hypoaminoacidemia is documented to occur in all cases of SND in which plasma amino acids have been measured, regardless of associated disease, makes it likely that this metabolic derangement is directly contributing to the cutaneous lesions seen in affected dogs.

Clinical Presentation

The disease is typically diagnosed in older dogs. Upon review of the literature, the mean age of all reported cases is 10 years of age, with a range of 4 to 16 years. Male dogs comprise 64% of reported cases. Shetland Sheepdogs, West Highland White Terriers, Cocker Spaniels, and Scottish Terriers may have a predisposition to develop HCS as they appear to be overrepresented (Outerbridge et al. 2002).

The most common clinical sign is the development of visually distinctive skin lesions with a characteristic distribution. In a recent review of all published cases, 94% of dogs had affected footpads with marked crusting, fissuring, and ulcerations (Outerbridge 2010). These footpad lesions are highly suggestive of SND (Figs. 11.4 and 11.5). Erythema, crusting, exudation, ulceration and alopecia can also involve the periocular or perioral regions, anal–genital regions, and pressure points on the trunk and limbs. The skin lesions in dogs with HCS may precede any other clinical signs. Secondary cutaneous infections with bacteria, yeast (i.e., *Malassezia, Candida*) or dermatophytes, particularly involving the feet, are often present in dogs with SND. Lameness secondary to footpad lesions, inappetance, and weight loss can also be associated with SND. Polydipsia and polyuria may be present when there is concurrent diabetes mellitus or if significant liver dysfunction is present.

Histopathologic findings of representative skin biopsies are unique and confirm the diagnosis. These findings include a marked parakeratotic epidermis with striking inter- and intracellular edema, keratinocyte degeneration in the upper epidermis, and hyperplastic basal cells that create the characteristic “red, white, and blue” histologic lesion. Evaluation of serum biochemistry panels often

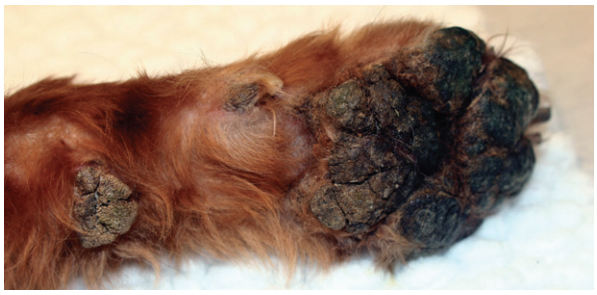


Fig. 11.4. Foot pad lesions in a dog with superficial necrolytic dermatitis (SND).

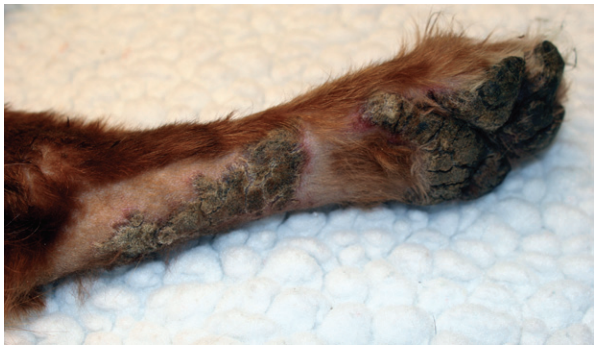


Fig. 11.5. Adherent crusting over pressure point on the tarsus and severe hyperkeratosis of the foot pads with fissures in a dog with SND.

demonstrates an increase in liver enzyme activities and a decrease in serum albumin concentration. Serum bile acid evaluations are abnormal in about half of affected dogs. A review of all reported cases found hypoaminoacidemia in all dogs, elevated glucagon in four out of four dogs that had a glucagonoma, and increased serum insulin concentrations in eight out of eleven dogs (Outerbridge 2010).

Abdominal ultrasound may demonstrate a unique "honeycomb" pattern to the liver consisting of variably sized hypoechoic regions surrounded by hyperechoic borders. Hepatic histopathology often documents a distinctive vacuolar hepatopathy with parenchymal collapse. Grossly, the liver may appear irregular, have multiple nodules, and be mistaken for being cirrhotic. There exists some contradiction as to whether the hepatic lesions in SND reflect true cirrhosis. Despite some histological descriptions of micronodular cirrhosis, one study, using special stains, confirmed only a minimal increase in collagen within portal areas (Gross et al. 1993). Extensive fibrosis and reduced liver size characteristic of chronic cirrhosis is not seen in livers that only have the hepatic lesion associated with SND.

Diagnosis and Treatment

Diagnosis of HCS is based on obtaining skin biopsies with the typical histopathologic changes. The characteristic dermatohistopathology can be focal within a given lesion. Whenever possible, multiple representative samples should be obtained and submitted. Biopsies should be chosen, if possible, from easily accessible sites and attempts to avoid general anesthesia should be taken, since these dogs are not often good candidates for anesthesia. The documented occurrence of abnormal laboratory findings, which can include elevated liver enzymes (i.e., serum alkaline phosphatase, alanine transferase) or hyperglycemia if concurrent diabetes mellitus is present, should increase the clinical suspicion of SND in dogs with compatible cutaneous lesions. If abdominal ultrasound is available, it can provide further support for the diagnosis if the characteristic "honeycomb" pattern is documented. If this ultrasonographic pattern to the liver is not visualized in a dog with a confirmed histologic diagnosis of SND, evaluation for a possible pancreatic tumor is necessary. Pancreatic tumors may not be readily visible with an abdominal ultrasound examination so measurement of plasma glucagon is also recommended. If plasma glucagon concentrations are abnormally increased or a pancreatic mass is visible on ultrasound the option for exploratory laparotomy and tumor excision can be considered. However, postoperative morbidity and mortality have been high. Plasma amino acids, if measured, should document a characteristic severe hypoaminoacidemia.

The most effective symptomatic or palliative therapy for dogs with HCS appears to be the administration of intravenous amino acids. A number of amino acid solutions are commercially available. There are a number of crystalline amino acid solutions for parenteral administration on the market that vary in their concentration and the inclusion of electrolytes. Although there are minor differences in the amounts of essential and nonessential amino acids between manufacturers there are no data to suggest that one product is more efficacious than another. Solutions without additional electrolytes are preferred. The following have all been used for intravenous infusions in treating dogs with SND: 10% Aminosyn IV solution (Abbott Labs, North Carolina); Travasol 8.5% without electrolytes (Baxter Healthcare Corp., Clintec Nutrition Company, Deerfield, IL); and ProcalAmine (3% amino acids with 3% glycerine and electrolytes (B. Braun Medical Inc., Irvine, CA).

Administration of 10% aminosyn at 25 ml/kg over 6 to 8 hours that is repeated at 7- to 10-day intervals has been suggested (Byrne 1999). These hypertonic amino acid solutions should be administered via a central vein to diminish the chance of thrombophlebitis. Inducing a hyperosmolar state is possible if administration is too aggressive. Dogs should be watched for neurologic signs and the infusion discontinued if these occur. If compromised hepatic or renal function is present the administration of intravenous amino acids may exacerbate hepatic encephalopathy or augment increases in BUN. Such dogs warrant close monitoring with serial measurements of ammonia, BUN, and osmolality during intravenous amino acid administration. Some dogs show dramatic improvement in attitude with resolution of skin lesions after receiving amino acid infusions. There are no rigorously studied protocols for the administration of amino acid infusions in these dogs and repeat infusions are performed bimonthly, monthly, or when clinical signs return.

Oral nutritional support should include a high-quality protein diet that can be additionally supplemented with an amino acid powder. The best oral nutritional approach is not known, but hyperalimentation with protein is indicated unless the dog is known to have hepatic insufficiency as documented by an abnormal liver functions test. The dog with SND does not require protein restriction as is necessary for dogs suffering from hepatic insufficiency and hepatic encephalopathy. Zinc and essential fatty acid supplementation are often recommended, in part because of the reported initial improvement in some people with NME. Feeding egg yolks (three to six per day) has been anecdotally reported to result in clinical improvement in some dogs (Gross et al. 1993). This provides some additional protein but also possibly micronutrients that may have some as yet unknown role in this disease.

Secondary infections should be treated with appropriate antibiotic and antifungal therapy with careful consideration of those drugs that may be hepatotoxic or require hepatic metabolism. Topical therapy with antibacterial and antiyeast shampoos can also be of benefit in some dogs in helping to manage secondary infections.

Therapy with glucocorticoids is not recommended. Although anti-inflammatory therapy for the skin lesions may be of some benefit, the risk of precipitating or exacerbating diabetes mellitus in these dogs makes the use of glucocorticoids contraindicated.

The prognosis for dogs with SND is generally poor and the majority of dogs have survival times of less than 6 months. However, 20% of the dogs in a study were maintained for 12 months or more with oral protein hyperalimentation and periodic parenteral IV amino acid infusions (Outerbridge et al. 2002).

Cutaneous Adverse Food Reaction

"Food allergy" is a term that is often incorrectly utilized in veterinary medicine to describe all adverse reactions following food intake. Cutaneous adverse food reactions (CAFR) can occur as the result of an immunologic or a nonimmunologic response to a dietary ingredient. Nonimmunologic reactions to food include food intolerance or food idiosyncrasy but also include toxic reactions (i.e., histamine in scombroid fish poisoning) that are dose related, occur in any individual, and are associated with histamine, tyramine (old cheese), or bacterial toxins (Scott et al. 2001a). "CAFR" is perhaps a better term than "food allergy" as it is possible that in some patients that respond to changes in diet it may not, in fact, be avoidance of an adverse immunologic response that is occurring.

In human medicine IgE mediated type 1 hypersensitivity appears to play a role in the pathogenesis of food allergy in young children and is, in fact, the best defined immunologic mechanism causing food allergy (Sampson 1998). In man, food allergens are often glycoproteins with a molecular weight of 10–70 kDa; however, the exact molecular size of food allergens is not known for dogs and cats. The pathogenesis of CAFR in small animals is not well understood and an understanding of what immunologic mechanism is occurring is not known in the majority of cases of dogs or cats with CAFR. In the literature, type 1, 3, and 4 hypersensitivity reactions are stated to be possibly involved in causing CAFR in small animals (Verlinden et al. 2006; Gross et al. 2005). There are numerous potential food allergens and because of the large number of ingredients in a typical commercial pet food it is nearly impossible to implicate which one might be a causative allergen for each animal suspected of having a CAFR. Upon review of the literature, the most commonly implicated food allergens in dogs include beef, dairy, wheat, lamb, egg, chicken, and soy (Verlinden et al. 2006). In cats the most commonly implicated food allergens are beef, dairy, fish, chicken, and lamb (Verlinden et al. 2006). Some studies have shown that a significant number of dogs and cats (35–50%) had adverse reactions to more than one food ingredient (Harvey 1993; Patterson 1995; Jeffers et al. 1996). In humans with food allergies, some foods can exhibit cross-reactivity between proteins from similar sources (e.g., seafood, cereals, nuts). There is conflicting evidence as to whether this is clinically relevant in small animals. Some studies have shown that there was not a

cross-reactivity between milk and beef proteins (Jeffers et al. 1996) while another study does show that bovine immunoglobulin G (IgG) in milk may confer cross-reactivity to beef and possibly to proteins from other ruminants that may have shared immunoglobulin homology such as lamb (Martin et al. 2004).

CAFR is considered to be the third most common allergic skin disease in dogs after flea allergy dermatitis and atopic dermatitis. CAFR in the cat is reported to be second in frequency to flea allergy dermatitis. The exact incidence of food allergy/CAFR in small animals is unknown and is difficult to determine from the literature, but it has been reported as 1% of all skin disease (Scott et al. 2001a) and 10% of all allergic skin disease (Scott et al. 2001a). Another study reported 17.45% of dogs that went through an elimination diet trial had CAFR (Chesney 2001), and that CAFR was the cause of pruritus in 23% of nonseasonal pruritic dogs (Reedy et al. 1997). CAFR is seen more commonly in individuals with other allergies and reported information about incidence may be influenced by the type and prioritization of diagnostic evaluations utilized in reporting studies, as pruritus is a threshold phenomena.

Fig. 11.6. Erythematous pre-auricular areas and pinnae with evidence of self-trauma in a cat with confirmed cutaneous adverse food reaction.

Clinical Signs

There is neither gender nor age predilections for food allergy in dogs and while an increased risk in certain breeds has been reported, there is no statistical evidence of breed predilections, and any breed can be affected. One-third to one-half of dogs diagnosed with CAFR developed clinical signs before a year of age (Scott et al. 2001a). CAFR in the dog most commonly results in nonseasonal pruritus with secondary self-trauma that may be generalized or localized. The clinical signs of CAFR can be very pleomorphic and can mimic or be complicated by other dermatologic diseases including atopic dermatitis, flea allergy dermatitis, ectoparasitism, *Malassezia* dermatitis, and pyoderma. Primary skin lesions seen with CAFR can include erythema, papules, and pustules. Secondary skin lesions result from the self-trauma associated with pruritus and can include alopecia, erosions, excoriations, lichenification, and hyperpigmentation. Face, ears, paws, perineum, and ventrum are commonly involved sites. Pruritus in these areas may be demonstrated by foot licking or face rubbing in addition to scratching or chewing pruritic sites. Secondary pyoderma and *Malassezia* are common in dogs with CAFR. Otitis externa is a common manifestation of CAFR, and in some animals it is the only clinical sign.

CAFR in cats has no age or sex predilections. Siamese cats are reported to be at increased risk (Gross et al. 2005). Cats with CAFR can present with a number of reaction patterns. Pruritus is often very severe and centered on the face, neck, and pinnae (Fig. 11.6). Miliary dermatitis, eosinophilic plaques, eosinophilic granulomas, and feline lip ulcers may also occur in cats. Pruritus causing self-traumatic alopecia can also involve the limbs, ventral abdomen, and inguinal area. Otitis externa can also be a feature of CAFR in cats as it is in dogs.

Concurrent gastrointestinal (GI) signs may accompany pruritic skin disease caused by CAFR in small animals, but the reported incidence varies in the literature. It is estimated in most publications that fewer than 20% of animals with CAFR have concurrent GI signs (White 1998).

Diagnosis and Treatment

An elimination diet trial is the most important and only reliable diagnostic test to evaluate for and diagnose a CAFR in a dog or cat (Jeffers et al. 1991). This involves feeding a chosen diet for a period of time based on avoiding ingredients previously fed and then challenging the patient with the original diet. If clinical signs return upon rechallenge and abate again on the elimination diet a diagnosis of CAFR is made. A large commitment is required by the owner to successfully complete an elimination-and-rechallenge diet trial, but it is the only way to conclusively identify patients with adverse reactions to food. Neither serology nor intradermal testing provide clinically relevant information about which food proteins an animal

is allergic to. A number of studies have shown that serologic evaluation for IgE levels to dietary proteins has little to no clinical utility in predicting which dietary protein is acting as an allergen (Jeffers et al. 1991; Mueller and Tsohalis 1998; Scott et al. 2001a).

During an elimination diet trial all previous food items are removed and a new trial diet that meets certain criteria is chosen. The trial diet should contain a limited number of novel proteins or a hydrolyzed protein. It should also avoid vasoactive amines and meet the nutritional needs for that animal. There is no such thing as a "hypoallergenic diet." A diet can be nonallergenic to an individual if it contains ingredients that the animal has never eaten before. There are a number of options for trial diets to be used during an elimination diet trial. These include home-cooked diets with a single, novel protein and a novel carbohydrate component (see Chapter 8 on home-prepared diets), commercial uncommon protein diets that are novel for the individual animal, or commercial hydrolyzed protein diets. Which diet is chosen depends on the thoroughness and accuracy of the past diet history, special nutritional needs of the animal, palatability, and practicality for the owner. Home-cooked diet trials have the advantage that there is complete control as to what ingredients are being fed, and there are no additives or preservatives. However, they are very labor intensive and can be expensive, especially for large breed dogs, and not all animals will willingly eat home-cooked diets. Home-cooked diets often are not nutritionally balanced, which is a concern for certain life stages like growth. Although most are not nutritionally balanced, supplements are not needed during the short time of the elimination diet trial in adult dogs, but taurine should be added at 125–250 mg/kg body weight for cats undergoing a home-cooked diet trial. If chosen for long-term management of CAFR, the home-cooked diet must be balanced by a veterinary nutritionist or with commercially available software with appropriate nutritional supplements to provide all essential dietary needs for that individual (please see Chapter 8). Commercial uncommon protein diets are nutritionally balanced and are more practical for most owners. However, additives are present, and the antigenic properties of dietary ingredients may be altered during the processing of the diet in such a way as to make them more allergenic. Hydrolyzed diets are based on proteins that are hydrolyzed to smaller peptides and amino acids. This decreases the molecular size of the proteins consumed and hopefully the antigenicity and allergenicity of the protein is diminished. Although free amino acids are not allergenic, they are limited in their use in diets as they have a bitter taste and are hyperosmolar and can result in diarrhea. Most of the commercially available hydrolyzed protein diets are not based on uncommon proteins and not all of the protein within the diet is hydrolyzed. It is therefore possible for a hydrolyzed diet to fail to identify or manage CAFR. However, for the majority of animals with confirmed food allergy or CAFR, there is good evidence that hydrolyzed diets can control their clinical signs. Studies have shown that soy-sensitized dogs did not respond to oral administration of hydrolyzed soy protein (Jackson et al. 2003; Puigdemont et al. 2006).

Once the diet for use during an elimination trial has been chosen, based on the past diet history and the needs of the owner and animal, it is vital that the owner fully understands that the animal can have no access to any other food items. This includes all treats, human food items, foods given to hide oral medications, flavored toothpaste, and flavored medications or supplements including heartworm preventatives. It has been shown that food allergic dogs will react to the heartworm flavored preventative Interceptor® (milbemycin with pork liver and soy, Novartis) with increased pruritus and increased serum IgE within days of getting the medication (Jackson and Hammerberg 2002). It is important also to discuss with owners what strategies will be used to prevent access to the food if any other animals are in the household. Prior to starting a diet trial the animal should be evaluated for any concurrent secondary infections with bacteria and/or yeast and treated appropriately. Depending on geographic location of the animal it is also important to be sure that flea control is being used appropriately.

The elimination diet trial should be performed for a minimum of 6 to 8 weeks and ideally 10 to 12 weeks. The patient should be reevaluated after 4 weeks to ascertain if all infections have been adequately eliminated and reassess the intensity and distribution of pruritus. Although maximum improvement may take up to 10 to 13 weeks, significant improvement can be seen within the first 6 weeks provided all other concurrent diseases contributing to pruritus are also addressed (e.g., pyoderma, *Malassezia* dermatitis or flea allergy dermatitis). It is important to continue therapy for any concurrent dermatologic diseases during the rechallenge portion of the trial so that infections do not recur that could exacerbate pruritus and lead to erroneous interpretations of the rechallenge.

Up to 75% of dogs with CAFR will concurrently have other allergies (Scott et al. 2001a). Consequently, there may be only a partial improvement seen during the food trial. To prove if any decrease in the animal's pruritus is because of CAFR, a rechallenge needs to be done with the original diet. Animals with CAFR will have a recurrence

or exacerbation of their pruritus within hours to days, with most having a recurrence within 3 to 7 days. If after 2 weeks there is no change in the degree of pruritus, the animal does not have CAFR. The diagnosis of food allergy or CAFR is confirmed if the animal's pruritus returns or worsens, and the degree of pruritus again improves when the animal is placed on the novel protein diet.

In order to determine specifically what the offending allergen is requires provocation tests with single ingredients from the diet. If the animal is allergic to a particular food ingredient, pruritus will increase within 1 to 2 weeks after introduction of that ingredient. CAFRs are managed by avoidance of any offending dietary allergens confirmed with provocative testing or by strictly feeding a diet that is known to not induce CAFR.

Flowchart 11.1 presents an algorithm for evaluating CAFR with an elimination diet trial.

Cutaneous Xanthomatosis

The formation of cutaneous xanthomas is rare and often reflects underlying dyslipoproteinemia secondary to diabetes mellitus, therapy with megestrol acetate, or hereditary defects in lipid metabolism. Cutaneous xanthomas in cats have been reported with hereditary hyperchylomicronemia (i.e., lipoprotein lipase deficiency), megestrol acetate induced diabetes mellitus, or naturally occurring diabetes mellitus. Cutaneous xanthomas have been reported in dogs with diabetes mellitus. Affected animals may be consuming a diet rich in fats or triglycerides. Cutaneous xanthomas typically appear as multiple pale yellow to white plaques, papules or nodules with erythematous borders. They are often located on the face, ventral trunk, and over boney prominences. Larger masses may ulcerate and exude inspissated necrotic material. Cats with inherited hyperchylomicronemia may also demonstrate peripheral neurologic signs due to nerve compression from subcutaneous xanthoma formation. Histologic evaluation of skin biopsies reveals large foamy macrophages and giant cells. Serum biochemisty evaluations for diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia should be obtained. The feeding of a low fat diet and identification and correction of the underlying disturbance in lipid metabolism is recommended for patients that have had cutaneous xanthomas identified.

NUTRITIONAL SUPPLEMENTATION FOR MANAGEMENT OF SKIN DISEASE

Many dietary or nutritional supplements make claims to treat skin diseases and improve coat quality. The following section will review indications for the use of nutritional supplements in skin diseases and also which nutritional supplements may impact skin health and coat quality.

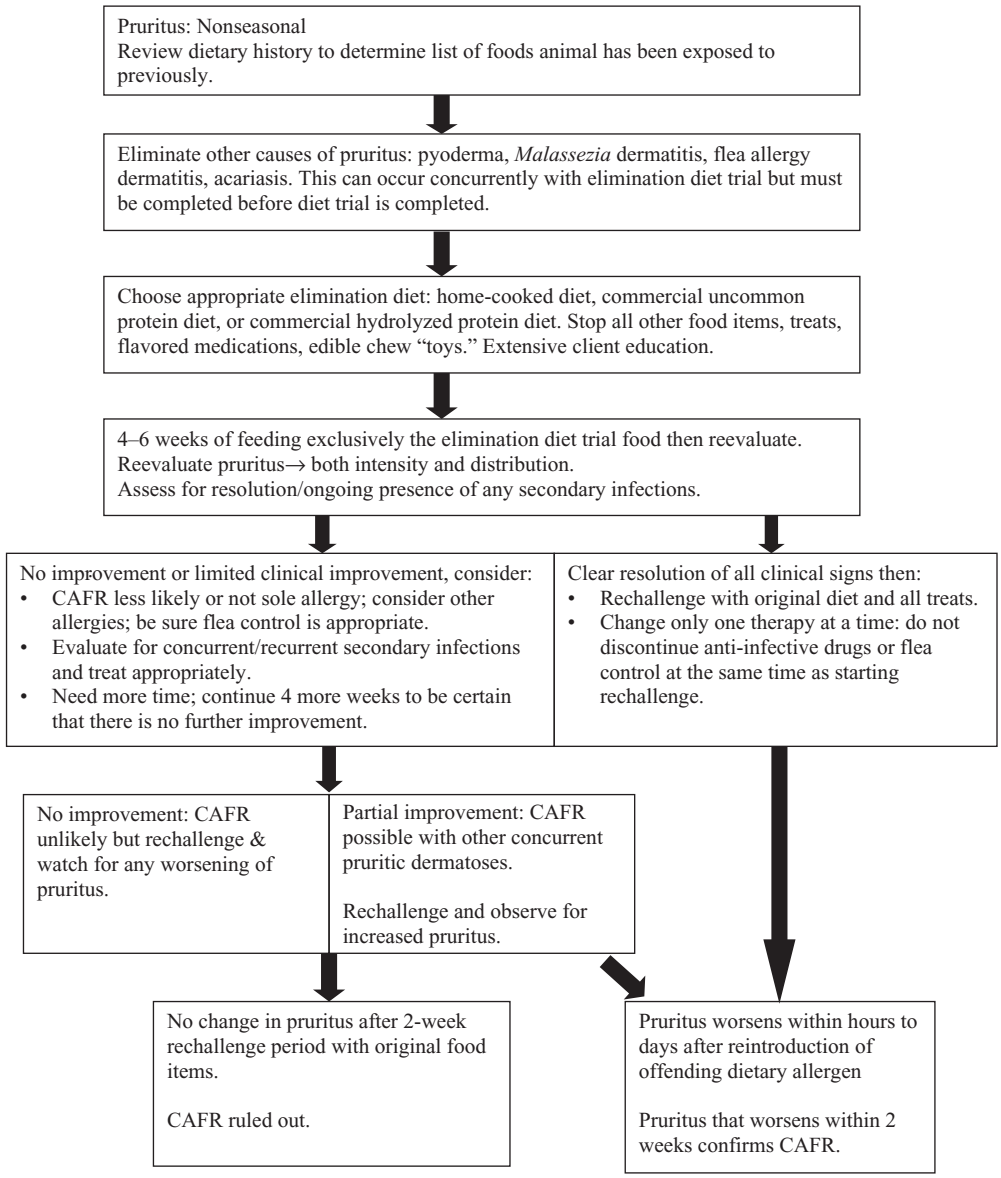
Vitamin A Responsive Skin Diseases

Vitamin A has been used to treat vitamin A responsive dermatosis seen in Cocker Spaniels and Miniature Schnauzers. There are numerous synthetic retinoids that have been developed and used for treating skin disease in humans and some have been used in small animals. The synthetic retinoids, either isotretinoin or etretinate, have been reported to be of benefit for treating primary idiopathic seborrhea, ichthyosis, solar or actinic dermatitis, sebaceous adenitis, infundibular keratinizing acanthomas, epitheliotropic T-cell lymphoma, and squamous cell carcinoma (Kwochka 1993). Due to the expense of these agents, vitamin A is often tried in the management of some of the above diseases. Anti-inflammatory corticosteroids can impair wound healing. Vitamin A and retinoids also significantly, but not completely, reverse some of the impaired wound healing seen with anti-inflammatory corticosteroids (Wicke et al. 2000).

Essential Fatty Acid Supplementation

EFA supplementation is commonly used in veterinary dermatology. Fatty acids have been reported to be beneficial in managing pruritus particularly in atopic dermatitis, feline eosinophilic reaction patterns (i.e., eosinophilic plaque, eosinophilic granuloma), cornification disturbances from a variety of causes, improving coat quality, and most recently for symmetric lupoid onychodystrophy. There are many open uncontrolled studies and only a few placebo-controlled or double-blinded crossover studies that have been published regarding the efficacy of EFAs in veterinary dermatology. Only trials with crossover design would minimize the lack of dietary standardization between different trials. Most of these trials investigated the supplementation of omega-6 EFAs for managing pruritus in atopic dermatitis. In the literature, the results of those crossover trials report variable efficacy ranging between 17% and 56% in managing atopic dermatitis in dogs (Olivry et al. 2001).

EFAs may have some efficacy in ameliorating pruritic skin conditions via a number of mechanisms. Certain PUFAs are thought to modulate eicosanoid production in the skin. Dihomogammalinolenic acid (DGLA) as well as the omega-3 fatty acid eicosapentanoic acid (EPA) can compete with arachidonic acid (AA) as substrate for cyclooxygenase(CO) and lipoxygenase (LO) enzymes. This results in the production of anti-inflammatory or less



Flowchart 11.1. Algorithm Evaluating for Cutaneous Adverse Food Reaction (CAFR) With Elimination Diet Trial.

inflammatory eicosanoids than those that are derived from AA. EFAs, in addition to modulating eicosanoid production, can influence the inflammatory response by altering cellular signaling and inhibiting cytokine secretion. More studies that look at controlled ratios of omega-6 to long-chain omega-3 fatty acids and amounts of long-chain omega-3 fatty acids are needed to fully understand their potential impact.

Supplementation with LA can cause a significant decrease in TEWL (Marsh et al. 2000). This suggests that omega-6 fatty acids can be incorporated in the intercellular lipids of the epidermis. Coat quality is positively affected by supplementation with EFAs as assessed by increased coat gloss and decreased scale (Marsh et al. 2000; Rees et al. 2001).

Essential fatty acids have been used to treat symmetric lupoid onychodystrophy in the dog (Bergvall 1998;

Mueller et al. 2003). They have been used as a sole therapy or in conjunction with other therapeutic modalities.

Zinc Supplementation for Skin Disease

The zinc responsive dermatoses have been discussed. Zinc has also been used in conjunction with essential fatty acids in a study to evaluate changes in skin and hair coat quality assessed by measuring coat gloss, presence of scale and TEWL (Marsh et al. 2000). The combination of zinc and linoleic acid produced statistically significant improvements in coat quality.

B Vitamins

Pantothenic acid and nicotinamide (B3) in combination with the amino acid histidine, choline and inositol were shown to reduce TEWL (Watson et al. 2006). Biotin supplementation has also been advocated to improve coat quality in dogs (Frigg et al. 1989).`

SUMMARY

- Dermatologic conditions associated with nutritional deficiencies are uncommon if the animal is being fed a diet that meets the nutritional needs for that individual.
- The skin has high needs for protein and energy.
- Essential fatty acids (EFAs) have multiple functions in the skin and are an important component of ceramides, which are necessary in maintaining the cornified lipid envelope or skin barrier.
- Zinc (Zn) is an important dietary element for the development of normal epithelialization.
- There are two syndromes of zinc responsive dermatosis seen clinically in the dog. Syndrome I is seen most commonly in Arctic breeds, and Syndrome II is seen in rapidly growing puppies, often fed poor-quality dog food. Both syndromes present with clinical lesions of adherent scaling around the mouth, chin, eyes, pinnae, and foot pads. Syndrome I dogs require oral zinc supplementation while Syndrome II dogs require a better diet.
- Generic dog food disease and feline pansteatitis associated with a diet low in vitamin E and high polyunsaturated fatty acids are two examples of how an unbalanced diet can cause cutaneous lesions.
- Superficial necrolytic dermatitis (SND) and cutaneous adverse food reactions (CAFR) are two skin diseases that can benefit from nutritional or dietary management.
- SND is a disease seen in older dogs and in association with a number of systemic metabolic disturbances including hypoaminoacidemia, possible diabetes mellitus, and in most cases a characteristic histologic and ultrasonographic hepatic pathology. Characteristic skin changes include hyperkeratotic foot pads and adherent crusting lesions over pressure points. Intravenous amino acid infusions may provide palliative management for some dogs.
- CAFR is a cause of nonseasonal pruritus in dogs and cats. It requires an elimination-and-rechallenge diet trial. Neither serology nor intradermal testing provide clinically relevant information about which food proteins an animal is allergic to.
- Nutritional supplementation with EFAs, vitamin A, and zinc may be beneficial in the management of certain skin diseases.

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Nutritional Management of Gastrointestinal Diseases

12

Nick Cave

INTRODUCTION

Perhaps no other organ system is so directly and immediately affected by nutrition than the gastrointestinal tract. Timing and frequency of feeding, route of feeding, and macronutrient and micronutrient compositions of the diet have profound influences on oral and intestinal health. In addition to the direct effect of diet on the body, there is a considerable indirect effect through dietary influences on the intestinal microflora. However, there are few controlled clinical trials that have evaluated specific dietary manipulation in either prevention or management of canine and feline gastroenteric diseases. As such, this chapter draws heavily from experimental models and from human gastroenterology. Practical recommendations have been made when possible, but as new evidence emerges, empirical, pragmatic suggestions will need to be questioned.

Key Dietary Variables

Protein

Dietary protein interacts with the gastrointestinal tract in several ways. It is a source of essential amino acids for the gastrointestinal tract, a source of dispensable amino acids for oxidation by the gastrointestinal tract, a source of energy and amino acids for the luminal flora, and a source of foreign antigens (Ames et al. 1999; Brandtzaeg 2002; Bounous and Kongshavn 1985). The digestibility of protein affects all these interactions. Protein digestibility is an inherent characteristic of the protein, but it also varies between animals in health, and notably in disease (e.g., exocrine pancreatic insufficiency), and is modified by food processing. Food processing can decrease the digestibility of protein by heating in the presence of simple carbohydrates (Dust et al. 2005; Bednar et al. 2000; Larsen et al. 2002). The glycosylation of amino acids, forming Maillard compounds, significantly reduces the efficiency of digestive enzymes and reduces the digestibility. Alternatively, some proteins that contain numerous cross-links that make them inherently poorly digestible proteins may be made more digestible through heating, which disrupts the three-dimensional structure (e.g., collagen).

Proteins (and amino acids) are also a key stimulus for the release of trophic hormones such as insulin, insulin-like growth factor-1 (IGF-1) and glucagon-like peptide-2 (GLP-2) (see below). Dietary protein affects motility in two main ways. First, the presence of protein in the stomach stimulates the release of gastrin, which promotes gastric, ileal, and colonic motility at the same time as ileocolic valve relaxation, as well as stimulating gastric secretion and having a trophic effect on the gastric and intestinal mucosa (Bueno and Fiormonti 1994; Hall et al. 1989; Lloyd 1994; Rehfeld et al. 2007; Strombeck and Harrold 1985; Thomas et al. 2003). The presence of dietary protein in the duodenum is also an effective stimulus for the release of cholecystokinin (CCK) from the proximal duodenum.

Dietary proteins also represent the largest source of dietary antigens, and are recognized and responded to by the mucosal immune system.

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Glutamine

Glutamine is a conditionally essential amino acid, and is utilized as a significant fuel source by mucosal leukocytes, in particular lymphocytes, and by small intestinal epithelial cells (Newsholme et al. 1987; Ziegler et al. 2003). In addition, it serves as the dominant nitrogen source for purine synthesis, the requirement for which is relatively large given the mitotic rate within the normal mucosa, and at an even greater rate during periods of mucosal repair. Many animal studies have demonstrated that enteral glutamine supplementation enhances gut mucosal growth and repair, decreases bacterial translocation and inflammation, and improves nitrogen balance in animal models of intestinal atrophy, injury, and adaptation (Ziegler et al. 2003; Kaya et al. 1999; Boza, Maire et al. 2000). Surprisingly perhaps, glutamine may be a more effective nutrient when incorporated into highly digestible proteins or small polypeptides than when administered as a free amino acid in solution (Boza, Maire et al. 2000; Preiser et al. 2003; Boza, Moennoz et al. 2000). This could be due to differences in utilization of glutamine by enterocytes or leukocytes, or it could be due to differences in the intestinal hormone-dependent trophic response to whole proteins rather than elemental diets. The difference between purified amino acid diets and whole foods was demonstrated in methotrexate induced enteritis in cats, where a glutamine-enriched purified diet was less effective than a complex diet in preventing bacterial translocation and villous atrophy (Marks, Cook, Griffey et al. 1997). Indeed, most studies found no benefit to supplemental glutamine over that provided by intact dietary proteins (Velasco, Hernandez et al. 2001).

Fat

Dietary fat is an important source of energy and is the macronutrient variable that determines the dry matter energy density of a diet. Animals with chronic intestinal disease are frequently malnourished from inappetance, maldigestion, and malabsorption, and thus may benefit greatly from higher energy dense diets. In addition, the absorption of dietary fat is required for the concurrent optimal absorption of the fat-soluble vitamins A, D, E, and K, as well as other fat-soluble nutrients (e.g., carotenoids, flavonoids). Long-chain polyunsaturated fatty acids also have functional effects as the precursors to eicosanoids (e.g., prostaglandins and leukotrienes) (Calder and Grimble 2002; Wander, Hall et al. 1997), as ligands for nuclear transcription factors [e.g., peroxisome proliferator activated receptors (PPARs)] (Kliewer, Sundseth et al. 1997), and as competitive inhibitors of lipopolysaccharide signalling via Toll-like receptors expressed by leukocytes (Lee, Plakidas et al. 2003; Weatherill, Lee et al. 2005).

The absorption of fat through intestinal lymphatics increases lymphatic flow rates and pressure, and luminal bile-acid fat micelles increase capillary permeability, resulting in a postprandial increase in intestinal lymphatic protein flux (Granger, Perry et al. 1982). Triacylglycerides (TAGs) are hydrolyzed in the intestinal lumen prior to uptake by the enterocytes, which absorb nonesterified fatty acids (NEFAs) and monoacylglycerides (MAGs) with the remaining fatty acid at the sn-2 position of the glycerol backbone. In rodents, the chain length of the NEFAs determines the proportion that is subsequently absorbed via lymph, versus the proportion that is absorbed directly into the portal veins bound to albumin. The percentage absorbed via lymphatics increases from less than 10% to 80% as chain length increases from capric acid (8:0) to lauric acid (12:0), while the MAG is still absorbed lymphatically (Mu and Hoy 2000). Thus, such medium-chain TAGs (6–12 carbon) increase lymphatic pressures and protein flux less than conventional long-chain TAGs. A similar effect has been noted in dogs, although it is less pronounced, and significant absorption of medium-chain TAGs via lymphatics still occurs (Jensen, McGarvey et al. 1994).

The presence of fat in the duodenum generates feedback signals to both the central nervous system (CNS) and to the myenteric plexus. Mediators of these signals include cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (NPYY). In the intestine, CCK-secreting cells, known as "I-cells," are located within the epithelium with their apical surfaces exposed to the lumen and are concentrated in the duodenum and proximal jejunum (Liddle 1997). CCK release from I-cells stimulates gall bladder contraction, pancreatic secretion, intestinal peristalsis, and inhibits gastric emptying and gastric acid production. In the cat, like dogs and humans, secretion of CCK by I-cells occurs in response to the luminal presence of long-chain triacylglycerides, proteins, and some amino acids (Backus, Rosenquist et al. 1995). The slowing of gastric emptying by small intestinal nutrients is associated with a reduction in proximal gastric tone, suppression of antral contractions, and stimulation of tonic and phasic pyloric contractions (Feinle, Rades et al. 2001; Heddle, Collins et al. 1989). The increase in phasic pyloric contractions is associated with cessation of transpyloric flow.

In addition to facilitating digestion in response to a meal, CCK is an important satiety signal, leading to meal cessation. Administration of CCK-receptor (CCK-1 receptors, formerly CCK-a receptor) antagonists before a meal delays satiety and prolongs feeding in rodents and humans.

CCK-1 receptor-deficient rats have prolonged feeding periods and are prone to obesity (Beglinger, Degan et al. 2001; Bi and Moran 2002). Rats treated with CCK during a meal stop eating and commence other activities such as grooming and exploration before resting or sleeping (Antin, Gibbs et al. 1975). In order for CCK to influence behavior there must be a direct or indirect connection between CCK and the CNS. It has been demonstrated that CCK mediates satiety in part by binding to receptors on vagal sensory afferent fibers innervating the stomach and small intestine and generating an ascending signal, rather than by the penetration of circulating CCK into the brain (Reidelberg, Hernandez et al. 2004). Surgical or chemical disruption of vagal transmission attenuates the satiating effects of CCK (Bi and Moran 2002).

In both dogs and cats, fat is a potent secretogogue for neuropeptides such as CCK. However, pharmacological inhibition of pancreatic lipase attenuates the effects of duodenal fat on reducing gastric emptying, on appetite, and CCK and GLP-1 secretion (Feinle, O'Donovan et al. 2003). Thus, fat maldigestion such as occurs in exocrine pancreatic insufficiency may contribute to maldigestion of other nutrients, independent of pancreatic function.

In humans with functional dyspepsia, dietary fat is frequently incriminated as an exacerbating and potentially causative factor that leads to exaggerated sense of fullness, nausea, and vomiting (Feinle, O'Donovan et al. 2003). This is supported by studies that demonstrate symptoms after duodenal lipid infusions, but not after isoenergetic infusions of glucose (Feinle-Bisset, Vozzo et al. 2004).

Fiber and Prebiosis

Dietary fiber has been defined as the edible portion of plants or analogous carbohydrates that are resistant to digestion and absorption in the small intestine, which are then available to be completely or partially fermented by resident microflora in the distal small intestine and large intestine (DeVries 2003). Most fibers are polysaccharides, although others, such as the polyphenolic compound lignin are not (Table 12.1). Restriction of the definition to plant-derived compounds omits indigestible carbohydrates derived from animal sources (e.g., chitin) or synthetic sources (e.g., fructooligosaccharides). Lastly, such a definition fails to include digestible carbohydrates that are in a form that is inaccessible to digestive enzymes (e.g., resistant starch). These compounds share many of the characteristics of fiber present in plant foods. Thus, a unifying definition of dietary fiber must be species-specific and incorporate all compounds that share the biological characteristics of fiber in the intestine. Dietary fiber can be classified according to physical or chemical characteristics, according to its effects on bowel microflora, or its

Table 12.1. Dietary Fiber Types

Fiber	Chemistry	Source
Lignin	Complex phenolic	Cell walls of woody plants and seeds
Cellulose	Linear, insoluble glucose polymer with β-1,4 glycosidic bonds	The main component of all higher plant cell walls
Hemicelluloses	Diverse group of polysaccharides containing hexoses and pentoses forming random amorphous structures	Found in almost all plant cell walls
Beta-glucans	Glucose polymers with a mixture of β-1,4 glycosidic bonds and β-1,3 glycosidic bonds	Oats and barley are rich sources
Pectins	Mostly a linear chain of α-1,4-linked D-galacturonic acid	Intercellular component of nonwoody plants, especially citrus fruits, apples, and some berries
Gums	A complex of viscous polysaccharides of varying types, and some glycoproteins	Seeds
Inulin and oligofructose (fructans)	Inulin is a mixture of fructose chains, oligofructose is a mixture of shorter fructose chains that may terminate in glucose or fructose	Energy storage compound of some plants, e.g., rhizomes
Resistant starch	Starch that is sequestered in plant cell walls or highly dehydrated and therefore, inaccessible to digestive enzymes	Bananas, legumes, raw potatoes. Can be formed during food processing by cooling and reheating.

effects on specific variables in the whole animal. In regard to its effects on gastrointestinal physiology and pathophysiology, the most important characteristics are viscosity, and fermentability.

Fiber Viscosity

Some types of soluble dietary fiber increase the viscosity of water when in solution and have the capacity to retain water within the viscous gel ("water-holding capacity"). This effect increases fecal water content and mass. Psyllium hydrocolloid (e.g., Metamucil®) has a greater water-holding effect than pea, oat, or sugar beet fiber (McBurney 1991). The formation of viscous gels slows gastric emptying, increases small intestinal transit times, slows the absorption, and reduces the digestibility of some nutrients (Ashraf, Lof et al. 1994; Bednar, Patil et al. 2001). Viscosity of ileal contents increases greatly with certain soluble dietary fibers (Dikeman, Murphy et al. 2007). This effect of fiber can be thought of as an antinutritive effect, and excessive dietary fiber may be counterproductive.

Although fibers that are soluble and capable of forming viscous gels are more likely to be fermentable, that is not always the case because the chemical requirements for both properties are different. The gel-forming component of psyllium seed husk, for instance, is not readily fermented by human colonic microflora and contributes significantly to its effect on increasing fecal bulk (Marlett and Fischer 2003).

The ability to form viscous gels in the stomach may be the mechanism by which dietary fiber facilitates the gastrointestinal transit of ingested hair. Dietary fiber (e.g., psyllium) has been shown to increase hair transit and decrease retching and vomiting associated with hairballs in chronically affected cats (Hoffman and Tetrick 2003; Dann, Adler et al. 2004).

Fiber as a Luminal Adsorbent

Fiber has long been recognized as an important luminal adsorbent of nutrients, bile acids, microbial toxins, and xenobiotics (Ebihara and Schneeman 1989; Floren and Nilsson 1982; Floren and Nilsson 1987; Ryden and Robertson 1997). Binding of xenobiotics may reduce intestinal or systemic exposure to carcinogens, while bile acid binding may be important for protection of the colonic mucosa from damage from unabsorbed bile acids.

Nonfermentable dietary fiber reduces bile acid solubility in fecal water and reduces the potential for interactions with the colonic epithelium (Ebihara and Schneeman 1989; Gallaher and Schneeman 1986). Bile acids can have a direct effect on the epithelium through their detergent effect. However, bacterial metabolites of bile acids ("secondary bile acids") can have other biological effects. Deoxycholic acid (DCA) and chenodeoxycholic acid have been reported to induce dysplastic changes, be cytotoxic, or even mutagenic to colonic epithelial cells. Luminal fiber directly protects the colonic epithelium by preventing direct interactions, reducing concentrations, and indirectly by the production of butyrate (Bartram, Scheppach et al. 1995). Wheat bran fiber (13.5–25 g/day for up to 12 months) can significantly lower both total and secondary (e.g., DCA) bile acid concentrations in the solid phase of human feces (Alberts, Ritenbaugh et al. 1996; Reddy, Engle et al. 1992).

Different fiber molecules can participate in hydrophilic and hydrophobic interactions. The diversity of structure and fermentability, and the chemical and structural changes that occur within the intestine alter binding capacities. Attempts to characterize the suitability of fibers for binding on the basis of simple physicochemical classifications are inadequate, and binding capacity for molecules of interest are best studied directly. Certainly crude fiber or total dietary fiber measurements are unreliable predictors (Table 12.2).

Fiber Fermentability

Just as the ability for mammals to digest polysaccharides is determined by the linkages between the monomeric subunits, so is the ability for intestinal microbes to hydrolyze and ferment dietary fiber. Dietary fibers undergoing bacterial degradation include polysaccharides such as resistant starch, pectin, inulin, guar gum, and oligosac-

Table 12.2. Analysis of Some Common Dietary Fibers

Fiber	Crude Fiber % DM	Total Dietary Fiber % DM	Soluble Fiber % DM	Insoluble Fiber % DM
Apple pectin	0%	85%	78%	7%
Citrus pectin	1%	82%	82%	0%
Beet pectin	0%	76%	76%	0%
Guar gum	2%	92%	83%	10%
Carrageen refined	0%	50%	44%	6%
Cellulose, (wheat)	63%	72%	0%	69%

Taken from Kienzle, Schrag et al. 2001.

charides [e.g., fructooligosaccharides (FOSs)] (Blaut 2002).

The extent to which fiber is utilized by microflora and the fermentative by-products produced is influenced by the structure of the carbohydrate and also the composition of the microflora within the individual. Complete fermentation will produce H_2, CO_2, and H_2O, while methane, acetone, proprionate, and butyrate will be produced during less complete utilization. Utilization of fructans by lactobacilli, *Escherichia coli*, and C*lostridium perfringens* is low, while oligofructose and inulin are more completely utilized by bifidobacteria (Cummings, Macfarlane et al. 2001). The effect of providing such substrate in the bowel lumen is to create a selection advantage to those species best adapted to its use. When the shift in microbiota has a positive effect on the host, the fiber is defined as a prebiotic. Proposed positive effects include reduction in mucosal adherence of pathogenic species, reduction in the numbers of pathogenic species, and immune modulation of the host (Blaut 2002; Bamba, Kanauchi et al. 2002; Schrezenmeir and de Vrese 2001; Guarner, Casellas et al. 2002).

Utilization of even the most fermentable fiber is never 100%, and most natural dietary fiber sources contain a range of carbohydrate structures. Thus, the fermentative by-products in dogs and cats will almost always contain short-chain volatile fatty acids (SCFAs) such as acetate, butyrate, and proprionate (Bednar, Patil et al. 2001). In particular, FOSs, inulin, and resistant starch lead to significant increases in the fermentative production of butyrate in dogs, while in both dogs and cats, SCFA production from other sources ranked from most to least is: citrus pectin, citrus pulp, beet pulp, cellulose (Sunvold, Hussein et al. 1995; Vickers, Sunvold et al. 2001).

Effects of Short-Chain Volatile Fatty Acids on the Colon

In most domestic species studied, including dogs, butyrate is oxidized by colonocytes, and in dogs is also oxidized by enterocytes (Marsman and McBurney 1995; Beaulieu, Drackley et al. 2002). It has been observed that when colonocytes are provided with butyrate, glutamine, glucose, and proprionate, the most used substrate is butyrate (Beaulieu, Drackley et al. 2002). In response to butyrate from fiber fermentation, colonocyte proliferation increases, intestinal mucosal weight increases, water and electrolyte absorption increases, and brush boarder enzyme activities increase (Farness and Schneeman 1982; Poksay and Schneeman 1983; Marsman and McBurney 1996; Forman and Schneeman 1982). SCFAs, butyrate in particular, stimulate longitudinal but not circular colonic smooth muscle contractions via a direct effect on smooth muscle and improve the aboral passage of feces in the colon (McManus, Michel et al. 2002). Luminal butyrate also increases mucin secretion, which reduces microbial adhesion and translocation and improves secretory IgA function (Barcelo, Claustre et al. 2000). Some effects may be concentration dependent, since at high concentrations, butyrate can also inhibit colonocyte proliferation (Marsman and McBurney 1995; Lupton 1995; Chapkin, Fan et al. 2000; Lupton 2004).

Effects of Butyrate on Intestinal Immunity

At reasonable physiological concentrations, colonic luminal butyrate suppresses the immune response by inhibiting the formation of the nuclear transcription factor NF-κB in colonocytes, endothelial cells, and resident leukocytes (Luhrs, Gerke et al. 2002; Yin, Laevsky et al. 2001). NF-κB regulates several cellular processes that vary according to the individual cell type and activation state, but includes adaptive and innate immune responses in the intestinal tract with several inflammatory cytokines and cell adhesion molecules under direct transcriptional control (Perkins 2007). The ability of butyrate to inhibit NF-κB activation and signaling appears to be the mechanism for the anti-inflammatory effect of butyrate in colitis (Luhrs, Gerke et al. 2002; Venkatraman, Ramakrishna et al. 2003). The nontoxic inhibition of lymphocyte proliferation may be a significant component of the immunological tolerance to large numbers of micro-organisms in the colonic lumen.

However, not all the beneficial effects of fermentable fiber can be reduced to the luminal production of butyrate. In a model of acute colitis in rats, feeding dietary inulin (a highly fermentable fiber) prior to the insult reduced signs and histological evidence of colitis, neutrophil recruitment, and eicosanoid production (PGE_2, LTB_4, and TXB_2) (Videla, Vilaseca et al. 2001). The administration of fecal water from inulin-fed rats via an enema had a similar effect. However, neither butyrate administered via an enema nor fecal water from inulin-fed rats had a significant effect on colitis in that model. Again, that suggests a more complex effect of dietary fiber on the mucosa than that explained simply by the production of volatile fatty acids (VFAs).

The effect of fermentable fiber on immunity is not limited to cells resident within the intestinal mucosa. Feeding the highly fermentable fiber pectin to rats affects lymphocytes isolated from mesenteric lymph nodes. The production of the Th_2-biased cytokines IL-4 and IL-10 by isolated lymphocytes is inhibited, consistent with a more Th_1-biased response compared with lymphocytes isolated

from cellulose fed rats (Lim, Lee et al. 2003). This suggests that lymphocyte activation within the mucosa in the presence of luminal fermentative by-products of fiber affects the immunophenotype of the cells that subsequently leave the intestine and recirculate to other mucosal sites. Thus dietary fiber may affect mucosal immunity throughout the intestinal tract, and probably at other mucosae as well.

Effect of Fiber on Intestinal Flora: Prebiosis

Certain fibers, such as the β-2 fructans (e.g., inulin, fructooligosaccharides), stimulate the growth and/or activity of intestinal bacteria such as *Lactobacillus* and *Bifidobacterium* species (Gibson, Beatty et al. 1995; Kaplan and Hutkins 2000). It has been proposed that increasing the numbers of these nonpathogenic species may have several direct effects including: (1) competition with pathogens for substrate; (2) interference with pathogen binding with, and competition for, epithelial binding sites; and (3) direct interaction with mucosal immune system.

Additionally, the short-chain volatile fatty acids might acidify the colonic lumen inhibiting species such as *Bacteroides* spp. and *Clostridia* spp. (Gibson and Wang 1994). Elimination of *Clostridium difficile* from the colonic flora within 6 days has been documented in mice by feeding a diet containing 20% fermentable fiber (Ward, Young et al. 1997). Similar effects on the fecal microflora have been seen in dogs given highly fermentable fiber (Grieshop, Flickinger et al. 2002). However, colonic microflora populations in dogs and cats may be relatively resistant to changes resulting from changes in dietary fiber intake (Simpson, Martineau et al. 2002).

Choice of Fiber

The combined effects of fiber fermentation with the absorptive effects of nonfermentable fiber make mixed fiber sources (e.g., psyllium) theoretically ideal for the management of colitis, over more completely fermentable fiber sources (e.g., hydrolyzed guar gum). In addition, the most highly fermentable fibers may also increase the production of methane, which has the capacity to disturb motility and exacerbate signs of colitis (see below). In other cases, more highly fermentable sources that produce higher concentrations of butyrate in the more proximal colon may be more effective than less fermentable sources of fiber. In a model of induced colitis in rats, both short-chain fructooligosaccharides and a resistant starch (retrograded high amylomaize starch) were evaluated for their ability to improve clinical and histological signs of colitis (Moreau, Martin et al. 2003). Only the resistant starch in that model improved the histological colitis score, and there was a trend toward more rapid resolution of the diarrhea, and less hematochezia. Clearly, the choice of fiber is important in certain disease states; however, insufficient information is available in feline and canine medicine to make any informed therapeutic recommendations beyond the initial introduction of mixed fermentable sources, and then proceeding with trial and error if required.

Table 12.3. Rich Sources of Dietary Fiber

Food source	Total Dietary Fiber % Dry Matter Basis	Total Dietary Fiber in 100 g As Fed
Oat bran (raw)	16%	15.4
Red kidney beans (cooked or canned)	28%	6.4
Baked beans (canned)	18%	5.0
Chickpeas (cooked or canned)	15%	4.4
Green peas (cooked)	23%	3.1
Pumpkin (cooked or canned)	29%	2.9

Taken from the United States Department of Agriculture Nutrient Database for Standard Reference, Release 18.

The addition of powdered products to diets can be easily achieved with moist diets, but often make dry diets unpalatable, even when mixed with water or stock. Ideal non-purified sources of fiber would be very concentrated in fiber, yet highly palatable, and easy to use as dietary supplements. Some suggested rich sources of mixed fermentable fiber are listed in Table 12.3.

Immune Response to Dietary Antigens (Oral Tolerance)

Immunological Basis for Oral Tolerance

Foreign dietary antigens interact with the intestinal immune system in such a way as to prevent unnecessary and detrimental immune reactions to them. In so doing, systemic immunity is rendered effectively unresponsive if the same antigen reaches the systemic circulation. This absence of reactivity to orally administered antigens is termed oral tolerance. Oral tolerance is generated in an antigen-specific and active manner that involves the induction of an atypical immune response.

Peyer's patches are the primary inductive area of the intestinal immune system. The specialized M-cells within the epithelium overlying the lymphoid follicles sample,

unspecifically or by receptor-mediated uptake, particulate and insoluble antigens, and whole micro-organisms (Brandtzaeg 2001). Antigens and organisms are then transported to leukocytes that reside within basal membrane invaginations, namely B-cells, macrophages, and dendritic cells. In the normal intestine these antigen presenting cells (APCs) lack co-stimulatory molecules such as CD80 and CD86. Antigens processed by these "unactivated" APCs are then presented to naïve B- and T-cells within the follicle, which then proliferate poorly. This occurs within a local microenvironment that differs from other sites in the body and results in induction of hyporesponsive Th3- or Th2-biased T-cells (Kellermann and McEvoy 2001). Activated cells then leave via lymphatics and pass via the mesenteric lymph nodes into the systemic circulation. They will then exit at mucosal sites via engagement of cellular adhesion molecules (CAMs) specifically expressed by the high-endothelial venules of mucosal tissues. Thus, activated or memory B and T lymphocytes enter the lamina propria to await a secondary encounter with their specific antigen.

The activated cells may secrete cytokines, but full differentiation into effector T-cells or plasma cells may not occur without secondary exposure. For both cell types to be re-exposed to antigen, intact antigens must reach the lamina propria. Intestinal epithelial cells are responsible for the absorption of antigen, release to professional APCs, and limited antigen presentation to cells within the mucosa on MHC class II. In the normal intestine, these secondary APCs will, like the primary presenters, lack co-stimulatory molecule expression and further add to the toleragenic environment. The effector T-cell clones resident in the normal intestine secrete a bias toward Th2 and Th3 cytokines, in particular IL-10 and TGF-β, thus directing B-cell isotype switching to produce IgA-secreting plasma cells, while inhibiting the development of Th1 lymphocytes and IgG production.

It is important that the immune system reserves the ability to rapidly respond to pathogens. This ability to recognize pathogenicity is based on the engagement of receptors that recognise evolutionarily conserved molecular patterns such as Toll-like receptors (TLRs), producing "danger signals." Predictably, expression of TLR-2 and TLR-4 is low to nonexistent in the mucosal cells of the normal human intestine, but they can be rapidly expressed in response to inflammatory cytokines (Abreu, Vora et al. 2001). The absence of these "danger signals" results in relatively inefficient antigen processing by intestinal APCs, markedly reduced or absent TNF-α/IL-1/IL-12 production, and the absence of CD80/86 co-stimulatory molecule expression. T-cells activated by such an APC will divide less, with most clones undergoing early deletion by apoptosis, while the surviving memory cells will tend to secrete IL-10, TGF-β, or no cytokines (Jenkins, Khoruts et al. 2001). This combination of apoptosis, functional defects in surviving clones, and T-cells secreting the anti-inflammatory and IgA-supporting cytokines is the general basis for immunological tolerance to luminal antigens.

Thus oral tolerance is composed of a delicate balance between induction of IgA, T-cell deletion, anergy, and immunosuppression; and the retention of antigen-specific lymphocytes capable of responding to invasive pathogens though antibody isotype switching to IgM, IgE, or IgG, and the production of inflammatory cytokines such as IFN-γ, IL-12, and IL-6.

Loss of Tolerance to Dietary Antigens

Loss of tolerance to dietary antigens will produce a conventional but detrimental immune response against the dietary antigen. Such an inappropriate response may produce inflammation locally, or at another anatomical site. The response will be characterized by one or a combination of:

1. Local cell-mediated inflammation.
   The resulting chronic stimulus may lead to lymphocytic intestinal infiltrates characteristic of inflammatory bowel disease.
2. Local antibody production of isotypes other than IgA.
   The production of IgE will lead to mast cell priming and intestinal hypersensitivity, i.e., food allergy with gastrointestinal signs (vomiting and/or diarrhea).
3. Systemic antibody production.
   Circulating IgE will lead to priming of mast cells at sites distal to the intestine such as dermal hypersensitivity, i.e., food allergy with pruritis as the clinical sign.

The initiating events that lead to loss of oral tolerance, or prevent it from developing, have not been described in either dogs or cats and remain poorly understood in any species. Suggested mechanisms include:

1. Increased mucosal permeability, e.g., following mucosal injury, or the neonatal intestine.
2. Co-administration of a mucosal adjuvant that activates and changes the phenotype of intestinal dendritic cells, e.g., bacterial enterotoxins.
3. Parasitism: Intestinal parasitism in cats leads to an exaggerated systemic humoral response that includes

increased production of IgE (Gilbert and Halliwell 2005).

Currently, there is speculation as to the importance of infections that stimulate a Th1-biased immune response in preventing Type-1 hypersensitivity reactions in people. This has been termed the "hygiene hypothesis," which states that a lack of maturation of the infant immune system from a Th2 to a Th1 type of immune response may be caused by less microbial stimulation in Western societies (Romagnani 2004). It is proposed that bacterial and viral infections during early life promotes a net shift of the maturing immune system toward Th1-biased responses, and reduce potentially allergenic Th2-biased responses. The assumed reduction in the overall microbial burden is supposed to allow the natural Th2 bias of neonates to persist and allow an increase in allergy.

The special role of parasites in modulating allergic responses to food and other allergens has been debated for half a century. Several older reports suggested that, similar to dogs and cats, parasitized humans are more likely to suffer from allergic diseases (Carswell, Merrett et al. 1977; Warrell, Fawcett et al. 1975; Kayhan, Telatar et al. 1978). In contrast to that is the higher incidence of allergic disease in Western populations and the growing incidence of allergic disease in developing nations. Elevations of anti-inflammatory cytokines, such as IL-10, that occur during long-term helminth infections have been shown to be inversely correlated with allergy. It has been suggested recently that the host's response to the parasite determines their predisposition to develop allergic diseases, and that the induction of a robust anti-inflammatory regulatory response (e.g., IL-10) induced by persistent immune challenge offers a unifying explanation for the observed inverse association of many infections with allergic disorders (Yazdanbakhsh, Kremsner et al. 2002). In either dogs or cats, the role parasitism and other infections that would fall within the hygiene hypothesis have yet to be defined in determining the development of food hypersensitivity. Since the immunological mechanism for the majority of food sensitivities may not be IgE mediated, the story may be even more complicated.

Food Immunogenicity

Adverse reactions to food are surprisingly common in both dogs and cats and have been reported to be present in up to 29% of all cases of chronic gastrointestinal disease in cats (Guilford, Jones et al. 2001). In addition, inflammatory bowel disease is the single most common cause of chronic gastrointestinal disease, and novel antigen and hydrolyzed protein diets are commonly reported to be effective in its management (Nelson, Dimperio et al. 1984; Guilford and Matz 2003). However, although the involvement of immunological mechanisms in a proportion of these adverse reactions is suspected, it is unproven. Indeed, the normal immunological response to ingested dietary antigens in cats has only recently been partially described (Cave and Marks 2004). Surprisingly, cats develop robust serum IgG and IgA responses to dietary proteins when fed as either aqueous suspensions or as part of canned diets, and it is likely that dogs are similar.

As obligate carnivores, felids have evolved on a highly digestible diet (Morris 2002). In keeping with this is the relatively short intestinal tract of the cat, which suggests that they may be poorly suited to poorly digestible diets. It is well established that the commercial canning process decreases protein digestibility and that this has biologically significant effects in cats (Kim, Rogers et al. 1996).

In rodents and rabbits, intact particulate and insoluble antigens are preferentially absorbed across the intestine through M-cells overlying the Peyer's patches (Frey, Giannasca et al. 1996). Classically, such antigens tend to invoke active immunity appropriate for micro-organisms. In contrast, soluble antigens have been found to be associated with oral tolerance (Wikingsson and Sjoholm 2002). It has also been shown that oral tolerance can be abrogated when soluble proteins are fed in oil-in-water emulsions, resulting in robust systemic humoral responses (Kaneko, Terasawa et al. 2000). This effect may also have relevance to the pet-food industry where interactions between dietary proteins and lipids in canned or extruded diets during the cooking and the manufacturing process could feasibly result in novel interactions not present in their native states.

In stark contrast to rodents is the intestinal response in chickens, where particulate antigens induce tolerance, while soluble antigens provoke active immunity (Klipper, Sklan et al. 2001). If the physical nature of the proteins within the natural diet of a species dictates how the intestinal immune system has evolved, this might have special relevance to species that are commonly fed diets different from their ancestors.

Commercial pet foods are subjected to significant heating during the manufacturing process. The effect of heat treatment on proteins is mostly to change the three-dimensional conformation of the protein. Although this may disrupt some antigens, it may equally uncover previously hidden antigenic determinants, or create new ones. Other reactions that occur at high temperatures include the Maillard reactions, which involve the reactions between

certain amino acids, and the reduction of sugars to produce less digestible compounds called melanoidins, which give a characteristic brown color. Melanoidins tend to be less digestible, less soluble, and certain melanoidins have been shown to be more "allergenic" than the original uncooked protein (Maleki, Chung et al. 2000; Maleki, Viquez et al. 2003).

The effect of heating during the canning process on the immunogenicity of dietary proteins has been evaluated in cats (Cave and Marks 2004). Using soy and casein proteins, the canning process resulted in the creation of new antigens not present in the uncooked product. In addition, a product of heated casein induced a salivary IgA response that was not induced by the raw product. Thus, commercial food processing can qualitatively and quantitatively alter the immunogenicity of food proteins. Although the significance of this finding is uncertain at present, it emphasizes the need for feeding highly digestible proteins sources, or perhaps even hydrolyzed proteins, when enteritis is present.

ACUTE GASTROINTESTINAL DISEASE

Acute gastroenteritis is a common reason for presentation of cats and dogs to veterinarians. Common causes include bacterial toxin ingestion (e.g., staphylococcal enteritis), bacterial endotoxin production (e.g., *Clostridium perfringens* enteritis), viral enteritis (e.g., rotavirus, coronavirus, parvovirus), self-limiting infections (e.g., *Cryptosporidium felis* and parvum, *Coccidia* spp.), and adverse reactions to food. Because of the transient and non-life-threatening nature of many cases, the cause of the majority remains undetermined. Despite ignorance of the exact cause, standard therapy is instigated, of which dietary management remains the cornerstone.

Withholding Food for Acute Nonspecific Gastroenteritis

Standard dietary recommendations for dogs and cats with acute gastroenteritis have been to withhold food for 24–48 hours, followed by the introduction of small quantities of a "bland" diet fed four to six times per day for 3 to 7 days. These dietary recommendations have stood the test of time but are based on common assumptions rather than any specific research. Arguments frequently offered in support of withholding food are that it:

1. *Provides bowel rest.* It is presumed that the presence of ingesta and the physical and metabolic demands of digestion and absorption will delay recovery. In acute colitis, feeding can indeed increase the severity of signs. When there is significant colonic inflammation, the normal motor response to a meal is altered. When ingesta enter the colon during the late postprandial period, an excessive number of giant migrating contractions may be stimulated. These giant migrating contractions may be associated with postprandial abdominal discomfort and increased frequency of defecation (Sethi and Sarna 1991).

   However, fasting in a normal animal is associated with intense migrating motor complexes ("housekeeper" contractions) extending from the pylorus to the ileum (Hall, Diamant et al. 1983). These vigorous contractions, described as "hunger pains" by some humans, are inhibited by the presence of luminal nutrients (Defilippi 2003). In almost all cases of enteritis, regardless of the aetiology, there is decreased motility with delayed gastric emptying and reduced segmental contractions (Shi and Sarna 2004; Hotokezaka, Combs et al. 1996). Thus, fasting does not immediately provide physical bowel "rest," and in most cases, reduced motility or ileus is present. Feeding has been shown to decrease the development and duration of ileus from various intestinal insults. A recent meta-analysis on the recovery of human patients following a wide range of abdominal surgical procedures demonstrated that early introduction of feeding resulted in shorter time to the presence of bowel sound and a trend toward shorter hospital stays (Charoenkwan, Phillipson et al. 2007). At worst, continuing oral feeding will have no detrimental effect on motility, and at best it will promote normal motility and prevent ileus.
2. *Reduces the risk of vomiting.* It has been suggested that vomiting is less likely to occur in the fasted state than the fed state, and that withholding food until vomition has decreased or stopped is important to reduce the risk of aspiration. The early introduction of enteral feeding in dogs with severe hemorrhagic gastroenteritis did indeed result in increased vomiting when a hydrolyzed protein diet was initially introduced, despite being fed at below maintenance rates (Will, Nolte et al. 2005). Nonetheless, vomiting decreased rapidly in the fed group and dogs were tolerant of enteral feeds within 2 to 3 days.

   In contrast, the prokinetic effect of feeding may decrease the emetic response. In dogs with parvoviral enteritis, the time to cessation of vomiting following admission was significantly shorter when forced feeding was instigated, compared with dogs that were fasted orally (Mohr, Leisewitz et al. 2003). Additionally, the luminal presence of a complex diet supports

mucosal integrity and decreases the magnitude of an enteric insult. Cats that were fed a complex diet did not vomit when given a toxic dose of methotrexate, while cats fed a purified diet did vomit.

However, foods that prolong gastric retention, especially high-fat diets and highly viscous diets [high soluble fiber (see below)], or diets that contain poorly digestible starch may promote emesis (Heddle, Collins et al. 1989; Meyer, Elashoff et al. 1994; Lin, Kim et al. 1992). Maldigestion can lead to distension and stimulation of the gut that increases the chance of vomiting. Predictably, gastric retention times increase with increasing meal size, but also with increased dry matter content (Goggin, Hoskinson et al. 1998).

Thus feeding can have either an emetic or antiemetic effect. Small frequent feedings have been recommended in order to limit the duration of acid secretion at each meal and to minimize gastric distension which can provoke nausea when the stomach is inflamed.

3. *Increases bacterial proliferation.* Undigested food provides nutrients for luminal bacterial fermentation and proliferation. However, fasting increases the rate of bacterial adherence and translocation in most experimental models (Marks, Cook, Griffey et al. 1997; Bark, Katouli et al. 1995; Tenenhaus, Hansbrough et al. 1994). In addition, acidification of the lumen through the production of volatile fatty acids (e.g., butyrate, proprionate) can make the environment less suitable for pH-sensitive pathogens such as *Campylobacter* and *Clostridium* spp. (Cummings, Macfarlane et al. 2001).
4. *Decreases osmotic diarrhea.* Unlike acute diarrhea in humans, the majority of cases of canine and feline diarrhea are not thought to involve a significant secretory component. Although this may be simplistic, it appears that the osmotic effect of unabsorbed nutrients and endogenously derived osmols are more important as contributors to the diarrhea. With almost any mucosal insult the absorptive capacity of the intestine is reduced and exudation may be increased. Undigested fat is susceptible to oxidation, hydroxylation, and the formation of by-products that can increase intestinal secretion, and increase vascular permeability, fluid secretion, and duration of diarrhea (Ramakrishna, Mathan et al. 1994).

It can be seen that the arguments presented above can be rebutted, or satisfied by optimal feeding. Thus the long-held belief in the value of bowel rest for the treatment of diarrhea has been challenged by the benefits of "feeding through" diarrhea. Recent studies of acute diarrhea in several species have shown that feeding through diarrhea maintains greater mucosal barrier integrity.

Benefits of Luminal Nutrition in Acute Gastroenteritis

Even in the absence of enteritis, fasting for even as short a period as 1 day in rats causes a significant decrease in villous height and/or crypt depth in the jejunum, ileum, and, to a lesser extent, colon (Ziegler, Evans et al. 2003; Kudsk 2003). In addition, fasting is associated with gut mucosal cell impairment marked by decreased levels of reduced glutathione (GSH), the major intracellular antioxidant, enhanced permeability to macromolecules, increased bacterial translocation from the lumen, and increased rates of enterocyte apoptosis (Jonas, Estivariz et al. 1999). Even with total parenteral nutrition, after 14 days of oral fasting in cats, small intestinal villous atrophy, and fusion and infiltration of the lamina propria with lymphocytes, plasma cells, and neutrophils occurs (Lippert, Faulkner et al. 1989). Thus oral fasting alone, and in the absence of nutritional deficiency, induces an intestinal insult.

Fasting also significantly reduces the specific activity and expression of certain digestive enzymes in the small bowel mucosa such as disaccharidases, which can lead to impaired digestion following the reintroduction of food (Holt and Yeh 1992). Transient lactase deficiency is common, particularly after rotavirus gastroenteritis (Zijlstra, Donovan et al. 1997). Occasionally it persists, and lactose intolerance may be a cause of post-gastroenteritis diarrhea. Gastric and pancreatic secretions are markedly reduced following a period of undernutrition (Winter 2006).

Generalized malnutrition, protein depletion, or deficiencies of specific nutrients, including essential fatty acids, folate, zinc, vitamin A, and vitamin B12 inhibit the growth and turnover of the intestinal mucosa. It has long been recognized that small intestinal enterocytes utilize luminally derived glutamine as their main oxidative fuel (see above). In addition, glutamine provides the carbon skeleton and amino nitrogen required for purine synthesis and hence is critical for normal DNA synthesis involved in enterocyte turnover.

Oral supplementation with zinc improves histological recovery, normalizes absorption, decreases permeability, and decreases NF-κB nuclear binding in experimental models of diarrhea (Altaf, Perveen et al. 2002; Sturniolo, Di et al. 2001). Additional mechanisms for the effect of zinc treatment on the duration of diarrhea include improved absorption of water and electrolytes, increased levels of

brush border enzymes, and faster regeneration of the intestinal epithelium.

Intestinal Recovery and Adaptation

Multiple factors, including luminal nutrients, pancreaticobiliary secretions, and humoral agents, have been implicated in controlling the intestinal adaptive response after an intestinal insult. Despite the multifactorial regulation of intestinal adaptation, luminal nutrients are fundamental to the adaptive response such that recovery is minimized or prevented in the absence of luminal nutrients. This conclusion is largely based on studies that show significant adaptive intestinal regrowth in rats and dogs fed orally compared with those fed parenterally following an intestinal resection. Indeed, even in the absence of an intestinal insult, total parenteral nutrition (TPN) causes dramatic intestinal atrophy in dogs, cats, rats, and humans (Lippert, Faulkner et al. 1989; Renegar, Johnson et al. 2001; Thor, Copeland et al. 1977). This fasting-induced atrophy is accompanied by inflammatory cell infiltrates in the lamina propria, increased intestinal permeability, and increased bacterial translocation.

The ileum, and to a lesser extent the colon, is important in intestinal adaptation and recovery. The ileum and colon are the primary intestinal sites of synthesis and secretion of glucagon-like peptide-2 (GLP-2) and insulin-like growth factor-1 (IGF-1) (Dube, Forse et al. 2006). GLP-2 is a 33 amino acid peptide hormone released from the intestinal endocrine cells (L-cells) following nutrient ingestion. GLP-2 exerts trophic effects on the small and large bowel epithelium via stimulation of cell proliferation and inhibition of apoptosis (Ljungmann, Harmann et al. 2001). GLP-2 also decreases gastric acid secretion and decreases antral contractions, thus contributing to the "ileal brake" (Wojdemann, Wettergren et al. 1998). In experimental models of intestinal disease, GLP-2 reverses parenteral-nutrition-induced mucosal atrophy and accelerates the process of endogenous intestinal adaptation following major small bowel resection (Ljungmann, Hartmann et al. 2001; Chance, Sheriff et al. 2000; Sangild, Tappenden et al. 2006; Drucker, Deforest et al. 1997). GLP-2 also markedly attenuates intestinal injury and weight loss in mice with chemically induced colitis, and significantly reduces mortality, bacterial infection, and intestinal mucosal damage in mice with indomethacin-induced enteritis. IGF-I production by the ileum produces a similar increase in enterocyte proliferation, an expansion of the proliferative compartment in the crypt, inhibits enterocyte apoptosis, and increases enterocyte migration (Dube, Forse et al. 2006). Thus luminal nutrients are essential for maximal and rapid mucosal recovery which is stimulated largely by enterically derived GLP-2 and IGF-1.

Effect of Luminal Nutrients on Inflammation

It has long been known that the immunological derangements that accompany malnutrition cannot all be prevented when nutrients are delivered parenterally (Dionigi, Ariszonta et al. 1977). A lack of luminal nutrients results in an increased expression of proinflammatory adhesion molecules, especially ICAM-1 (Fukatsu, Lundberg et al. 1999). This results in an increased number of primed neutrophils adhered to the microvasculature throughout the intestinal tract where they are able to contribute to oxidative and enzymatic tissue damage following activation. Fasting or TPN results in decreases in IL-4 and IL-10 that correlate with decreases in IgA and increases in ICAM-1 (Fukatsu, Kudsk et al. 2001). Lack of enteral feeding impairs the coordinated system of sensitization, distribution, and interaction of T- and B-cells important in the production of IgA, in the maintenance of normal gut cytokines, and in the regulation of endothelial inflammation (Kudsk 2003; Renegar, Johnson et al. 2001; Ikeda, Kudsk et al. 2003; Johnson, Kudsk et al. 2003). Thus the lack of luminal nutrients has been described as a "first hit" and increases the inflammatory response to a secondary insult in the gastrointestinal tract (GIT), but also the lungs, liver, and potentially other organs as well.

Glutamine

The amino acid glutamine reverses many of these defects and favorably influences the proinflammatory effects of gut starvation (Kudsk, Wu et al. 2000). The source of supplemental glutamine can influence gut mucosal glutamine concentrations, suggesting differences in its availability or utilization. Glutamine-rich intact proteins such as casein, whey, and soy appear to be more effective in increasing mucosal glutamine content than glutamine-enriched solutions (Marks, Cook, Reader et al. 1999).

Arginine

Arginine is an essential amino acid for cats because of their inability to synthesize sufficient quantities in the fasting state. However, beyond its role as an essential intermediate in the ornithine cycle, dietary arginine has long been known to enhance certain aspects of immunity. L-arginine is oxidized to L-citrulline + •NO by nitric oxide synthase. The inducible form within leukocytes (inducible nitrous oxide synthase, or iNOS) produces much greater amounts of •NO than the constitutive

endothelial (eNOS) or neuronal (nNOS) forms. The production of •NO after induction of iNOS in an activated phagocyte is limited mostly by the availability of free arginine. Therefore any increase in available arginine will increase the •NO produced by any given inflammatory stimulus (Eiserich, Patel et al. 1998).

Nitric oxide is a free radical. However, compared with other free radical species, in physiological conditions the molecule is relatively stable, reacting only with oxygen and its radical derivatives, transition metals, and other radicals. This low reactivity, combined with its lipophilicity, allows the molecule to diffuse away from its place of synthesis, and function as a signalling molecule on an intracellular, intercellular, and perhaps even systemic level.

Nitric oxide is required for normal intestinal epithelial maturation. It may be the principle inhibitory neurotransmitter in intestinal motility and is essential for the maintenance of normal mucosal blood flow. In addition, •NO inhibits the expression of cellular adhesion molecules, limiting unnecessary leukocyte entry, especially into the mucosal tissues. Nitric oxide inhibits T-cell proliferation, decreases NF-kB activation, and induces a Th2 bias to local responses. However, in contrast to the paradigm that •NO inhibits the key proinflammatory transcription factor NF-κB, some studies have suggested that iNOS inhibition can increase proinflammatory cytokine production.

As mentioned, •NO is relatively unreactive with nonradical molecules. However, reaction with superoxide (O2•–) to form peroxynitrite (ONOO–) is diffusion limited. Peroxynitrite is not a free radical, though it is a powerful oxidant, and has been shown to elicit a wide array of toxic effects ranging from lipid peroxidation, protein oxidation, and nitration leading to inactivation of enzymes and ion channels, DNA damage, and inhibition of mitochondrial respiration (Virag, Szabo et al. 2003). The cellular effect of ONOO– oxidation is concentration dependent; for instance, very low concentrations will be handled by protein and lipid turnover and DNA repair, higher concentrations induce apoptosis, whereas very high concentrations induce necrosis. Since both •NO and O2•– are produced in sites of inflammation, it is reasonable to propose that ONOO– might be involved in the pathogenesis of many cases.

In light of differences in the radius of effect of both O2•– and NO, colocalization of both molecules within the same cell would be expected to lead to disease. In this context, the finding that iNOS is capable of generating O2•– in conditions when L-arginine is unavailable is significant. This has been demonstrated recently in macrophages, where limiting L-arginine availability resulted in the simultaneous production of functionally significant amounts of O2•– and NO, and the immediate intracellular formation of ONOO– (Xia and Zweier 1997).

The large number of conflicting studies evaluating the role of •NO in inflammatory disease has resulted in a polarization of viewpoints between those who argue •NO is protective and those that argue it contributes to pathogenesis. This is unfortunate since both views are probably correct. The fate of any individual molecule of •NO is determined by multiple variables that determine its role in pathogenesis including:

- Site of production
- Timing within the local disease process that the molecule is produced
- Amount of •NO produced
- Redox status of the immediate environment
- Chronicity of the disease

Overall, it appears that supplemental arginine, either parenterally or orally administered, enhances the depressed immune response of individuals suffering from trauma, surgery, malnutrition or infection. This action is presumably through its ability to augment the production of •NO by iNOS in activated neutrophils and macrophages.

However, in cases of severe sepsis (i.e., infection accompanied by a systemic inflammatory response), augmentation of •NO production might be detrimental because of its effect as a negative cardiac ino- and chronotrope, its ability to inhibit coagulation, and its potent venous and arterial dilator effects (Suchner, Heyland et al. 2002).

Most commercial enteral nutritional formulas suitable for feeding to cats contain 1.5 to 2 times the minimum requirement of arginine for growth. However, supplementation of diets for intensive care nutrition has frequently been recommended and is widely used in human medicine for enhancement of the immune system in critical care. Although clinical improvements in some studies have been reported, critically ill patients with systemic inflammatory response syndrome, sepsis, or organ failure may actually deteriorate as the result of arginine supplementation (Stechmiller, Childress et al. 2004). Thus there may be cases where supplementation with arginine, beyond that provided by a conventional protein source may be beneficial, while in other cases it may be detrimental.

Intestinal Permeability

Even short periods of enteral fasting result in an increase in intestinal permeability in humans (Hernandez, Velasco

et al. 1999). Early refeeding of dogs and cats with acute gastroenteritis has been shown to reduce the increase in intestinal permeability that occurs in response to inflammation and apoptosis (Mohr, Leisewitz et al. 2003; Marks, Cook, Reader et al. 1999). Some of the effect of luminal feeding may come from the luminal provision of glutamine alone, which can restore enterocyte glutathione concentrations and protein synthesis, and normalize intestinal permeability. Even in single layer cell cultures of enterocytes, the application of glutamine to the apical (luminal) membrane normalizes permeability to a large molecular weight molecule, whereas applying glutamine to the basal membrane (simulating parenteral nutrition) does not (Le Bacquer, Laboisse, et al. 2003).

Veterinary Evidence

The effect of early enteral nutrition has been evaluated in dogs with severe parvoviral enteritis and in cats with severe mucosal damage from methotrexate toxicity. Early enteral nutrition in canine parvovirus reduced the time for normalization of demeanor, appetite, vomiting, and diarrhea, increased body weight, and may have improved mucosal permeability compared with the traditional approach of fasting until resolution of vomiting (Mohr, Leisewitz et al. 2003). In methotrexate-induced enteritis, feeding a complex diet abrogated the proximal small intestinal atrophy and bacterial translocation associated with feeding an amino-acid-based purified diet and was associated with a marked attenuation of the clinical signs associated with the toxicity (Marks, Cook, Reader et al. 1999). In contrast, when dogs that presented with severe hemorrhagic gastroenteritis were fed a commercial dry hydrolyzed protein diet soon after presentation, there was an initial increase in the frequency of vomiting, despite being fed at below maintenance rates (Will, Nolte et al. 2005).

Thus early reintroduction of feeding does not seem to exacerbate disease even in severely affected animals, and complex diets appear to be superior to purified diets in some models. However, clinicians must make individual decisions about the risks and benefits of feeding in patients with persistent vomiting. The risk of aspiration of vomitus is significant in patients that are moribund or unconscious, and in patients with concurrent dysphagia or laryngeal dysfunction.

Recommendations

It can be seen then that not only can the traditional concerns of feeding in acute gastroenteritis be allayed, but there are considerable arguments for not delaying feeding at all. The current recommendations are for oral rehydration over a period of 3 to 4 hours as required, followed by immediate reintroduction of oral feeding. However, it is unlikely that attempting to feed the daily maintenance energy requirements (MERs) is a sensible approach in the short-term management of dogs and cats suffering from acute diarrhea and certainly not in cases of frequent vomiting. Therefore, if only 25% of the animal's resting energy requirements (RERs) is fed as a highly digestible, low-fat diet, mucosal recovery may be optimized, and exacerbation of diarrhea or vomiting minimized. This has led to the concept of "minimal luminal nutrition."

At the current point of understanding, the ideal dietary characteristics would be:

1. *High digestibility.* This is easier to recommend than it is to specifically practice. Most commercial high-quality dry diets would qualify, as would many home-prepared ingredients. For protein sources, cooked fresh chicken or fish, cottage cheese, or egg would qualify. Cooked white rice or potato is a suitable carbohydrate source, although rice may be superior (see below). Commercially canned diets generally have a lower digestibility than dry diets, often have a high fat or viscous fiber content, and thus cannot be recommended over a similar dry product. However, there is no evidence that the difference in digestibility has any clinically measurable consequences.
2. *Low fat.* No fat-titration studies have been performed to guide firm recommendations. However, a pragmatic recommendation would be to choose the lowest fat content available. An almost arbitrary cutoff of 20% of metabolizable energy (ME) could be made.
3. *Novel antigen content.* For acute gastroenteritis, strict adherence to protein novelty is not prioritized over other considerations and simple avoidance of the staple dietary protein sources of the particular patient is prudent, without being excessive. Some hydrolyzed protein diets are also excellent choices (Cave 2006).
4. *Dietary fiber content.* Some fermentable fiber is almost always beneficial, while excessive contents can exacerbate delayed gastric emptying, diarrhea, flatulence, and abdominal pain. An empirical recommendation is to select diets that contain less than 8% total dietary fiber or less than 5% crude fiber.
5. Initial feeding should not exceed 25% of the calculated RERs, divided into three feeds per day. This amount can be rapidly increased with clinical improvement.

Examples of suitable home-prepared recipes are presented in Table 12.4.

Table 12.4. Suitable Home-Prepared Diets for the Short-Term Management of Acute Gastroenteritis in Dogs and Cats

Cottage cheese and rice	
Cottage cheese (1% milk-fat)	1 unit
Boiled white rice	1 unit
ME density: 4.8 kJ/g or 1 kcal/g as fed	
Nutrient composition (% of ME):	
Digestible protein	33%
Fat	6%
Carbohydrate (and ash)	61%
Chicken and rice	
Boiled chicken breast (skin and visible fat removed)	1 unit
Boiled white rice	4 units
ME density: 5.5 kJ/g or 1.3 kcal/g as fed	
Nutrient composition (% of ME):	
Digestible protein	26%
Fat	6%
Carbohydrate (and ash)	68%

Therefore, these diets possess ideal macronutrient profiles, are highly digestible, and are highly palatable. There may be an advantage to the use of boiled white rice as the carbohydrate source in diets for acute gastroenteritis. A small molecular weight (<1.5 kDa) lipophilic, nonprotein compound isolated from boiled white rice inhibits the activity of chloride secretory channels in intestinal epithelial cells, which is increased in secretory diarrhea (Mathews, MacLeod et al. 1999). This so-called rice factor may be responsible for the improvement of oral rehydration solutions in humans with diarrhea when rice is incorporated (Gore, Fontaine et al. 1992; Alam, Ahmed et al. 1992).

Few commercial diets are currently available that could be considered ideal in all respects for acute nonspecific gastroenteritis, and commercial formulations change such that firm recommendations cannot be made. Most commercial diets both provide significantly more fat (>25% of ME) but are complete and balanced. In addition, when feeding as little as 25% of RER, it is unlikely that the fat content will be sufficient to exacerbate vomiting or diarrhea if less than 30% of ME is composed of fat. The evaluation of diets formulated around protein hydrolysates such as Hill's z/d, Nestle-Purina HA, and Royal Canin Hypoallergenic warrants further study. Despite the greater than ideal fat content, the combination of high digestibility and reduced antigenicity make them attractive options for the management of acute gastroenteritis.

CHRONIC GASTROINTESTINAL DISEASE

Periodontal Disease

Periodontal disease can be considered the scourge of domesticated dogs and cats because of its prevalence, the morbidity it is associated with, the expense of treatment, and the hassle of prevention. In a study in North America of 31,484 dogs and 15,226 cats of all ages, the prevalence of calculus and gingivitis was around 20%. Predictably, "dental disease" was the most commonly reported disease (Lund, Armstrong et al. 1999). In another study it was found that 80% of dogs older than 6 years had moderate to severe periodontitis (Hamp, Olsson et al. 1984). The frequency of "marginal periodontitis" was found to be 82.3% in dogs aged 6 to 8 years, 82.9% in dogs aged 9 to 11 years, and 95.7% in dogs aged 12 to 14 years.

These are staggering figures and give (one-sided) support to the hypothesis that a natural diet protects against periodontitis, while commercial and soft homemade diets lead to periodontitis in almost all animals eventually. We imagine the effects of chewing skin, connective tissue, and bone—and the teeth cleaning effects these actions have—and we assume that periodontal disease occurs with a low frequency in the wild because selective pressure over the millennia would have produced animals that were resistant to such disease when consuming their normal diet. In contrast, when we feed domestic cats and dogs dry extruded diets, or perhaps worse, rolls or canned diets, it is intuitive that periodontal disease would be more common in those animals, whose teeth are not being naturally cleaned by their diet.

It is clear that periodontitis will develop in almost all animals fed standard commercial diets, which do not have other regular measures to prevent the disease. Even more so, softer diets appear convincingly to be worse. Cats fed dry food develop less calculus and gingivitis than cats fed exclusively canned food (Studer and Stapley 1973). In a large survey of domestic cats in Japan, calculus was more common in cats fed canned or home-cooked meals than cats fed dry foods (41% vs. 25%) (Survey on the Health of Pet Animals 1985). Similarly, it was shown many years ago that soaking dry food prior to feeding is a reliable method of inducing the rapid formation of plaque, calculus, gingivitis, and eventually periodontitis

in dogs (Burwasser and Hill 1939). In a study of dogs in Brazil, those that were fed diets of home-prepared foods and scraps had significantly more dental disease than those fed commercial dry diets (Domingues, Alessi et al. 1999).

Additionally, when commercial diets are supplemented with more abrasive, "natural" ingredients, the development of periodontitis is retarded, or even prevented. Feeding raw oxtails as a supplement to a dry food has been shown to be effective in minimizing the development of gingivitis and periodontitis in long-term (>6 years) studies in Beagles (Brown and Park 1968). Once weekly feeding of oxtails was shown to remove existing calculus to 5% of previous amounts within 2 weeks and to maintain them at that level for years. Further, a diet consisting of raw bovine trachea and attached tissues was much more effective in reducing plaque, calculus and gingivitis than the same diet when fed minced (Egelberg 1965a).

Thus, commercial diets are associated with periodontal disease, and softer diets are worse than dry diets, though perhaps there is less difference between the two types of commercial diet than one might expect. In addition, the supplementation of commercial diets with "natural" chews, such as oxtails, dramatically improves oral health.

These conclusions are consistent with the hypothesis that dogs and cats that consume commercial diets have a very high risk of eventually developing periodontal disease. So what evidence is there that a "natural" diet protects against periodontal disease in feral or wild dogs and cats?

Periodontitis in Feral and Wild Animals

The skulls of 29 African wild dogs were examined for evidence of periodontal disease, as a model for the domestic dog "natural" diet (Steenkamp and Gorrel 1999). The diet of these dogs is almost exclusively small antelope. Wild dogs have shorter maxillae than wolves, making them tend toward brachygnathism, and the upper 3rd premolar is often rotated to make room for the other, overlapping PMs. This gives a more powerful bite but may predispose to periodontitis. Signs of teeth wearing was seen in 83% of teeth, and 48% of skulls had fractured teeth, with signs of endodontic disease in half of those. There was evidence of periodontitis in 41% of dogs, but interestingly, mild calculus deposits were found on only two skulls. Therefore, the wild dog on a "natural" diet is affected by dental disease at similar rates to domesticated dogs, and, surprisingly, the "natural" diet does not protect against dental disease. This is despite its efficacy at preventing the formation of calculus.

In a study of feral cats on Marion Island, the skulls of 301 cats that had been trapped and killed were examined (Verstraete and van Aarde et al. 1996). Evidence of periodontitis was found in 61.8% of cats and in 14.8% of teeth. Again, however, calculus was found on only 9% of cats and on 0.76% of teeth—consistent with their diet, which was mostly birds (95% of diet). Therefore, the cause of periodontitis is unclear, but it is not prevented by natural diet or by preventing calculus formation. In contrast, odontoclastic resorptive lesions were infrequent, with 14.3% of cats affected and 1.2% of teeth.

In a recent study in Australia, there was significantly less calculus on the teeth of 29 feral cats that consumed a diet of rats, mice, lizards, birds, and insects than on a sample of 20 domestic cats fed dry or canned food (Clarke and Cameron 1998). However, once again, there was no difference in the prevalence of periodontal disease between the two groups.

These studies then, throw considerable doubt on the central hypothesis. Although it appears than a "natural" diet protects against, or at least minimizes, the development of calculus, it does little to protect against the development of periodontitis and tooth loss, in either cats or dogs.

This then leads us to ask two questions: (1) What, if any, chewing activity protects against periodontitis, and (2) how can there be any dissociation between the development of calculus and periodontitis? Or put another way: Is protection against the formation of calculus different from protection against periodontitis?

Evidence of the Protective Effect of Chewing Activities

In a survey of 1350 client-owned dogs in North America, the association of calculus, gingival inflammation, and periodontal bone loss with chewing activity was analyzed (Harvey, Shofer et al. 1996). It was found that there was progressively less accumulation of calculus, gingivitis, and periodontal bone loss in dogs given access to a variety of chewing activities. Although this study also suggested that rawhide chews were the most effective, no chewing material was consistently effective in all dogs. Access to bones was associated with protection against calculus and gingivitis but still did not protect against periodontitis in premolars or molars in general. These disparities could be due to differences in chewing techniques, or could represent differences between dogs, unrelated to the act of chewing.

In prospective trials evaluating specific chews, the results are again consistent with the realization that plaque and calculus might be reduced, but not prevented, and that such reductions do not necessarily translate to protection against

gingivitis or periodontitis. In a relatively long-term trial, 38 mixed breed dogs were fed a dry diet plus Pedigree Denta Rusk® 6 out of 7 days, for 21 months. Both plaque and calculus were reduced (15–20%), but there was no reduction in gingivitis after 18 months (Gorrel and Bierer 1999).

In another study using a different "multi-ingredient" chew for 4 weeks, plaque was reduced by 38%, gingivitis by 39%, and calculus by 49%. The addition of a proprietary antimicrobial to the chew did not further the benefit (Brown and McGenity 2005). In an evaluation of rawhide chews, the development of plaque over 7 days while feeding a dry diet was reduced by approximately 20% by daily chewing on one rawhide chew (Hennet 2001).

Using the C.E.T.® Forte chews daily as a dietary supplement to cats for 4 weeks, plaque was reduced by 20%. There was a 40% reduction in calculus, but no significant reduction in gingivitis. Also, only 6 out of 15 dogs consumed the chews every day (Gorrel, Inskeep et al. 1998). In a further study of the C.E.T.® Forte chews, the chews were added in pieces, 3 hours after the morning meal. After 4 weeks there was a 64% reduction in calculus, a 15% reduction in plaque, but a nonsignificant reduction in gingivitis (Ingham, Gorrel et al. 2002).

Feeding Hill's t/d® for 6 months reduced plaque by 39% and gingivitis by 36% in 20 mixed breed dogs (Logan, Finney et al. 2002). In a comparison of feeding Hill's t/d®, with a normal dry diet plus a daily Pedigree Chum Rask®, there was no difference in the efficacy of reducing plaque, calculus, or gingivitis between the two (Rawlings, Gorrel et al. 1997).

So in none of these studies has a product or diet been shown to have 100% efficacy, and some do not demonstrate any benefit in the scores of gingivitis. In no trials have the interventions been long enough to demonstrate any efficacy in preventing the development of periodontitis.

Dental Diets

Since the arrival of Hill's t/d®, several food companies have produced diets with claims of benefits to dental health. Such diets are either formulated to abrade the teeth (Hill's, Nestle-Purina, Iams), or contain additives that function as inhibitors of calculus formation (Royal Canin), as antibacterials (Royal Canin), and as plaque retardants.

Sodium hexametaphosphate (HMP) forms soluble complexes with most cations and reduces the availability of calcium for incorporation into plaque to form calculus. It has been proposed that the HMP-calcium complexes are then "washed away" in the saliva. The calcium then disassociates within the acid environment of the stomach, and HMP does not reduce dietary calcium bioavailability. The addition of an HMP solution to a dry diet reduced calculus formation in dogs by almost 80% when softened biscuits were fed (Stookey, Warrick et al. 1995). However, no long-term studies have been performed to demonstrate that reducing calculus formation in such a manner has any effect on the long-term production of gingivitis or periodontitis in dogs or cats. From the studies mentioned above, one would not be hopeful.

High concentrations of ascorbate inhibit the growth of several species of oral bacteria *in vitro*. A stable form of vitamin C (sodium ascorbyl phosphate) has been added to an experimental diet and fed to cats. After 28 days, plaque and calculus were reduced slightly, and the development of gingivitis was almost completely prevented compared with the control group (Wehr, Elsbett et al. 2004). Other attempts to control oral bacteria include the addition of green tea polyphenols (Royal Canin), which have been shown to have *in vitro* antibacterial activity against important oral pathogens. To date, no studies have been performed to confirm their *in vivo* efficacy.

Clearly, although most "dental diets" have some proven efficacy, they are inadequate to prevent periodontitis in the long-term, despite significantly reducing calculus. It is likely that combinations of approaches will have additive effects (e.g., a dental diet plus rawhide chew plus occasional bones), but this remains untested.

There is a trend, therefore, that reducing, or even preventing, the development of dental calculus is insufficient to prevent gingivitis and is presumably insufficient to prevent the development of periodontitis in either dogs or cats. This applies to experimental means, and the "natural" diet.

There does not seem to be a clear or simple relationship between the amount of plaque, and especially the amount of calculus on a tooth and the severity of gingivitis associated with it. Some studies have shown a reduction in gingivitis in the absence of calculus reduction by adding dental chews (Rawlings, Gorrel et al. 1998), while others have demonstrated a reduction in calculus and plaque with no appreciable reduction in gingivitis (Gorrel, Inskeep et al. 1998).

Therefore, mechanical debridement or simply reducing plaque or calculus formation is unlikely to be the panacea for the prevention of dental disease. So do all these approaches fall short because they are unable to effectively remove plaque, or because simply removing or preventing plaque is insufficient to prevent gingivitis and periodontitis?

The Effect of Gingival Stimulation

Tooth brushing has long been held to be the gold standard of oral care in dogs and cats and is effective in the long-

term, even in reversing preexisiting oral disease. Daily tooth brushing can return gingivae to health in naturally occurring gingivitis, and daily brushing prevented plaque and gingivitis in a 4-year study (Lindhe, Hamp et al. 1975). In dogs with "perfect" oral health, brushing three times weekly is sufficient to maintain gingival health for 24 weeks, whereas once weekly is not (Tromp, Jansen et al. 1986). The same group then evaluated the effect of frequency of brushing once gingivitis was established and found that daily (but only daily) brushing would normalize the gingivae (prior to the development of calculus). Gorrel and Rawlings (1996) found that brushing every other day was insufficient to prevent plaque and gingivitis from developing within 4 weeks in dogs fed a dry food, but this was improved significantly if a dental chew was added. A subsequent study demonstrated that the addition of 0.2% chlorhexidine to the chew reduced plaque accumulation but had no further benefit to preventing the development of gingivitis (Rawlings, Gorrel et al. 1998). This emphasizes the importance of the effect of mechanical stimulation of the gingivae to prevent gingivitis.

Mechanical stimulation of the gingivae by tooth brushing enhances proliferation of fibroblasts, collagen synthesis, and a reduction in gingivitis in dogs. When daily tooth brushing, including brushing of the gingivae, was compared with removal of plaque with a supragingival curette in dogs fed a softened diet, tooth brushing reduced inflammatory cell infiltration into the gingival tissues, increased fibroblast proliferation and collagen synthesis after 5 weeks (Horiuchi, Yamamoto et al. 2002). In addition, a greater effect of brushing was seen with twice daily than once daily brushing (Yamamoto, Tomofuji et al. 2004). This difference was apparent despite the complete prevention of plaque accumulation by use of the curette.

Mechanical stimulation by tooth brushing has been found to enhance pocket oxygen tension, decrease exudation, increase microcirculation in gingivae, and increase saliva flow following the induction of gingivitis in dogs (Tanaka, Hanioka et al. 1998). If the rate of gingival tissue turnover and desquamation is increased, access to the gingival tissues of the sulcus may be reduced. Thus the mechanical stimulation by brushing contributes to the prevention of periodontal pocket formation and can promote epithelial reattachment.

The Influence of Diet on Saliva and the Flora

Normal saliva contains lysozyme; myeloperoxidase; lactoperoxidase; lactoferrin; and histatins, a group of small peptides that bind to hydroxyapatite and can kill *Candida albicans* and *Strep. mutans*, and are inhibitory for *Porphyromonas gingivalis*, *Prevotella*, and *Bacteroides* spp. Saliva also contains IgA and leukocytes, and probably has a "flushing" effect, inhibiting the attachment of bacteria to the gingival tissues. In dogs, synthetic, topically applied histatin preparations can significantly inhibit the development of experimental gingivitis (Paquette, Waters et al. 1997).

Animals maintained on liquid diets develop salivary gland atrophy within days (Scott, Berry et al. 1990). The atrophy is rapidly reversible once a hard diet is reintroduced. The saliva secreted by such animals has a 50% reduction in protein content (Johnson 1984). These findings have been observed in animals from rodents to man. Therefore, food consistency affects the synthesis of salivary proteins and the volume of saliva produced. In humans, an inverse relationship exists between the lysozyme concentration in stimulated parotid saliva and the mass of plaque that develops in 48 hours (Jalil, Ashley et al. 1992).

In humans, modification of the diet to be of a firmer texture resulted in a 40% increase in the flow rate of stimulated parotid saliva, as well as an increased plaque pH, and salivary flow rates were significantly correlated with the bite force required to consume the diet (Yeh, Johnson et al. 2000). The flow rate of saliva is significantly increased when human subjects chewed four sticks of sugar-free gum per day for 8 weeks.

Interestingly, dogs fed a hard diet develop a different oral flora from those fed a soft diet—prior to the establishment of clinically apparent periodontitis. Fusiforms and spirochetes rapidly dominate the normal flora when a softened diet is introduced (Krasse and Brill 1960). Dogs that are fed via feeding tubes develop plaque and gingivitis as rapidly as those fed soft diets (Egelberg 1965b). Thus chewing modifies the oral environment in ways that are independent of a simple clearing or debridement activity.

Conclusions and Recommendations

The following conclusions can therefore be made:

1. Periodontal disease is the most common disease affecting domestic dogs and cats. Paradoxically, there is little evidence that the "natural" diet protects against periodontal disease.
2. Although chewing activities and dietary additives may be sufficient to reduce plaque or even prevent calculus, only those activities that provide appropriate gingival stimulation will prevent gingivitis and periodontitis.
3. Diet influences the oral flora and saliva and can thus influence the development of periodontal disease

independent of antiplaque or anticalculus activities. Animals that require prolonged or permanent tube feeding are at risk of rapidly developing periodontal disease.

4. Tooth brushing, recreational chewing, mouth rinsing, and the addition of the bacteriostat xylitol (note at high dose xylitol can result in hypoglycemia) to drinking water or mouth rinses should all be considered.

The data presented above clearly demonstrate that while helpful, no single individual dietary intervention is sufficient to prevent a disease that has an almost certainty of developing. Multiple strategies are required to minimize the risk of periodontal disease if regular tooth brushing is not practiced. For dogs, these might include feeding diets proven to reduce plaque and gingivitis development; providing therapeutic chewing activities; rawhide chews; bones large enough to be chewed on, but not chewed up; and dental toys. For cats, they might include proven dental diets, and chicken or turkey necks or wings that have been previously frozen, then seared on the outside quickly to reduce microbial contamination. Reasonable arguments against the practice of feeding bones include dental damage and intestinal trauma. However, in the author's practice, those adverse events have not been seen when poultry necks are fed. Future research must move toward understanding the relative importance of saliva production and composition, gingival stimulation, and oral microflora.

Esophageal Disease

Motility Disorders and Megaesophagus

Esophageal motility disorders can result from failure of sensory afferent pathways or from motor neuron or neuromuscular disease. Sensory afferent failure prevents the initiation of peristalsis when the food bolus enters the proximal esophagus such as occurs in idiopathic megaesophagus (Tan and Diamant 1987). In those cases, primary peristalsis is profoundly reduced and secondary peristalsis is not initiated. Firm, large food boluses that stimulate the esophagus are more likely to elicit contractions than soft food or gruels. In contrast, the neuromuscular dysfunction that accompanies myasthenia gravis prevents muscular contraction despite intact sensation. The differences in sensory and motor dysfunction between patients with esophageal disease probably dictates the physical properties of the food that is best tolerated. The food that best suits a given dog or cat with megaesophagus may be a liquid gruel, meat or dog roll chunks, or even kibble (Davenport, Remillard et al. 2010; van Geffen, Saunders et al. 2006; Guilford and Strombeck 1996). Thus experimentation, or evaluation of esophageal motility using barium admixed food and fluoroscopy is needed to identify the ideal food consistency for feeding dogs and cats with megaesophagus.

Recommendations

Elevated feeding to promote passage via gravity is usually recommended, whatever food is selected. When practical, the goal should be that the cervical and thoracic portions of the esophagus are elevated during, and immediately following, eating. Elevating a food bowl may raise the cervical portion but may still allow accumulation of food in the thoracic portion if that remains horizontal. Hand feeding chunks of meat or meat balls while the patient remains in a seated position is laborious but very effective. Experimentation with different food consistencies is recommended, if soft meat balls or chunks are not tolerated.

Esophagitis

Esophageal pain can be debilitating and lead to pronounced anorexia. In cases where oral feeding is not possible, gastrostomy tube placement is indicated. Where oral feeding is possible, a selection of soft food or even slurries is usually better tolerated than abrasive dry kibble. The main feeding concern for patients with esophagitis is the risk of promoting gastroesophageal reflux and exacerbating the esophagitis.

After a meal, food settles to the dependent part of the stomach body while gas bubbles coalesce and accumulate dorsally in the fundus and cardia, activating stretch receptors in the wall of the cardia (McNally, Kelly et al. 1964). Afferent vagal fibers (ventral branch of the subdiaphragmatic vagus nerve) arising from the cardia of the stomach (in the dog) induce isolated (i.e., in the absence of peristalsis) transient lower esophageal relaxations (TLORs) of the gatroesophageal segment (GES) (Sang and Goyal 2000; Martin, Patrikios et al. 1986; Reynolds and Effer 1988). These are relatively prolonged relaxations of the GES in the absence of swallowing that have a pattern distinctly different from swallow-induced lower esophageal sphincter relaxation (Wyman, Dent et al. 1990). The TLORs are elicited by gaseous distension of the cardia and not by fluid distension, nor by distension of the fundus (Strombeck, Turner et al. 1988; Straathof, Ringers et al. 2001). This reflex in response to the presence of gastric gas has been termed the "belch reflex." As gas is refluxed through the relaxed GES postprandially, leakage of gastric contents and acid may occur. Belching and acid reflux in normal human adults often occur simultaneously. In fact,

the majority of transient GES relaxations are accompanied by reflux, either of liquid, gas, or both (Sifrim, Silny et al. 1999). In the dog, liquid and gas reflux occur during transient GES relaxations that are very similar to those during reflux in humans (Patrikios, Martin et al. 1986).

Fat restriction has long been the most commonly recommended dietary adjustment for patients with esophagitis (Guilford and Strombeck 1996). This recommendation has been based on studies that have shown that the ingestion of fat decreases GES tone and the concern that it therefore increases the risk of gastroesophageal reflux. In humans, the GES tone decreases after ingestion of pure fat and a combined fat–protein meal, whereas ingestion of pure protein and glucose increases GES tone (Nebel and Castell 1973). Indeed the difference in fat content need not be great in some circumstances since whole milk but not nonfat milk lowers the GES tone in humans (Babka and Castell 1973). However, it has recently been observed that there is a difference between pure fat ingestion and whole foods. In experiments where GES tone has been measured following a meal in healthy humans, increasing energy density by increasing the energy from fat (up to 58% of ME) (Pehl, Waizenhohefer et al. 1999; Colombo, Mangano et al. 2002). In addition, when ingested volume and percentage of fat kJs or kcals remain the same, GES tone is no different when the total kJs or kcals ingested is increased by 50% (Pehl, Pfeiffer et al. 2001). The differences between these and earlier studies are probably the volume and total energy content of the fluids ingested.

As discussed above, distension of the gastric cardia initiates transient reductions in GES tone (TLORs) immediately postprandially. Increasing the volume of a meal enhances gastric cardia distension and increases the number of TLORs in the immediate postprandial period (Maher, Crandall et al. 1977). Increasing the osmolarity of an ingested yogurt solution from 145 mOsm/L to 500 mOsm/L while maintaining the same volume and fat content increases the rate of TLORs and gastroesophageal reflux by 50% in human patients with reflux disease (Salvia, Vizia et al. 2001). Similarly, increasing the volume by only 50% has an identical effect on the rate of TLORs.

Although the volume of the ingested meal appears to increase gastroesophageal reflux, the rate of gastric distension is more important than the end volume (Straathof, van Veen et al. 2002). Slow meal ingestion reduces the effect of volume on the rate of TLORs (Wildi, Tutuian et al. 2004).

Gastroesophageal reflux is commonly reported during high-intensity endurance exercise in otherwise healthy asymptomatic humans, and it is due to tonic reductions in GES tone (Maddison, Shepherd et al. 2005). Similar studies have not been conducted in dogs or cats, and in the absence of evidence it is prudent to assume that the case is similar in those species.

Recommendations

It is now clear that the most important variables that increase gastroesophageal reflux induced by a meal are volume, total energy content, osmolarity, rate of ingestion of the meal, and possibly postprandial exercise. However, gastroesophageal reflux is not affected by the fat content or energy density when the diet consumed is a complete food. On that basis it appears that the long-standing recommendations of feeding a low-fat diet may not be ideal. It is clear that frequent small meals are considerably better than single boluses and that slowing the rate of ingestion would be beneficial, if difficult or impractical. It may be that high-fat meals have the advantage that smaller volumes can be fed and reflux minimized. Until species-specific research answers this question, it is recommended that efforts be directed toward increasing the frequency of feeding, decreasing the volume of meals, elevation of the thoracic esophagus, avoiding high osmolarity foods such as hydrolysates, and that restriction of dietary fat not be prioritized.

Small Intestinal Disease

Chronic Intestinal Inflammation and Idiopathic Inflammatory Bowel Diseases

The inflammatory bowel diseases (IBDs) are the most common causes of chronic vomiting and diarrhea in dogs and cats 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 (Guilford 1996). 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, and neoplasia (Guilford 1996). Failure to eliminate known causes of gastrointestinal inflammation that can mimic IBD can result in a poor response to dietary or pharmacologic therapy.

The etiology of canine and feline IBD is poorly understood, but the main hypothesis for the etiopathogenesis of human IBD is that there is dysregulation of mucosal immune responses to intestinal microflora and/or dietary antigens (Guarner, Casellas et al. 2002; Magne 1992; Giaffer, Cann et al. 1991; Belsheim, Darwish et al. 1983). There is evidence from clinical observations and animal

models to incriminate normal luminal bacteria or bacterial products in the initiation and perpetuation of the disease (Rutgers, Batt et al. 1995). In addition, antibiotics are often empirically administered in cases of IBD as adjunctive or primary therapy, and there is widespread acceptance of their efficacy (Tams 1993; Jergens 1994).

Regardless of the underlying etiology for any given patient, abnormal immune responses to dietary antigens are often suspected, and the clinical response to novel protein diets supports that hypothesis (Nelson, Dimperio et al. 1984; Nelson, Stookey et al. 1988). Exaggerated humoral and cellular responses, and clinical food intolerance have been recorded in human IBD patients (Pearson, Teahon et al. 1993; van Den, Cahill et al. 2002; van Den, Kamm et al. 2001). Serum IgG concentrations specific to dietary antigens are consistently greater in dogs with chronic gastrointestinal disease than normal dogs, and fecal IgE specific to dietary antigens is consistently found in Soft-Coated Wheaten Terriers with IBD (Foster, Knowles et al. 2003; Vaden, Hammerberg et al. 2000). However, the frequency with which these might occur and the significance that immune responses play in the pathogenesis of canine and feline IBD are unknown.

Also unknown in any given patient is whether any abnormal immune response to the diet is the cause or result of a mucosal infiltrate. If abnormal immune response is the cause, it is expected that removal of the inciting antigen would lead to improvement. If abnormal immune response is the effect, it still may be that removing the largest single source of antigen during an elimination-diet trial is sufficient to reduce the inflammatory stimulus, allowing restoration of normal intestinal immunity.

Because of the consistent partial or complete response, restriction or manipulation of individual dietary components is perhaps the single most important factor in the treatment of IBD, and it may be sufficient in mild cases. Despite this fact, there is a paucity of information pertaining to the nutritional requirements of dogs and cats with IBD.

Nutritional Derangements in Chronic Inflammatory Bowel Diseases

Protein-Energy Malnutrition. The disruptions of absorptive area, normal epithelial function, permeability, and motility that occur with IBD result in disturbed nutrient absorption. Caloric insufficiency, intestinal protein loss, increased catabolism, and decreased absorption can result in hypoalbuminemia, panhypoproteinemia, and muscle wasting in a significant number of cases on presentation (Hart, Shaker et al. 1994). Similar findings are reported in humans with IBD, in whom protein-energy malnutrition has been documented to occur in 20–85% of IBD patients (Gee, Grace et al. 1985).

Magnesium. Hypomagnesemia has been identified in approximately one-third of canine and feline admissions to intensive care facilities when intestinal disease was the primary complaint (Toll, Erb et al. 2002; Martin, Matteson et al. 1994). Whether hypomagnesemia is a common feature of IBD on presentation has not been reported. However, the combination of malabsorption, anorexia, and therapy with magnesium free fluids (e.g., lactated Ringer's solution) is predicted to lead to hypomagnesemia. The possibility of hypomagnesemia should be suspected in cases if cachexia and hypokalemia are concurrently present and if intestinal ileus cannot easily be rectified.

Iron. Anemia is a relatively common finding upon presentation and can result from blood loss or systemic suppression of hematopoiesis. In addition, severe iron-deficiency anemia has been reported in conjunction with IBD in dogs (Ristic and Stidworthy 2002).

Vitamin B12 and folate deficiency. Low serum B12 and/or folate have been described in cats and dogs in association with a wide variety of gastrointestinal disease including IBD (Reed, Gunn-More et al. 2007; Simpson, Fyfe et al. 2001). In one study, cats affected with IBD apparently had a greatly decreased serum half-life of B12, which may have contributed to the deficiency (Simpson, Fyfe et al. 2001). However, not all authors have reported common B12 deficiency in cats with IBD. In one study in the United Kingdom, B12 deficiency was extremely rare, although only five cats with IBD were included (Ibarrola, Blackwood et al. 2005). In a further study of serum B12 and folate concentrations in cats with a variety of diseases in the United Kingdom, there was no association between the presence of gastrointestinal disease and serum B12 or folate concentrations (Reed, Gunn-Moore et al. 2007).

Cats with low serum B12, and with low B12/folate have been reported to have a lower body condition score than nondeficient cats (Reed, Gunn-Moore et al. 2007). It is likely that mucosal repair is impeded in the initial management of IBD when B12 is deficient and its absorption impaired. There is anecdotal evidence that the correction of the deficiency may reduce the requirement for immunosuppression or that the response to therapy may be limited until it is corrected. In a study of cats severely deficient in B12 with chronic intestinal disease, vitamin B12 supplementation resulted in increased weight gain, reduced vomiting, and reduced diarrhea in most cats (Ruaux, Steiner et al. 2005). Unfortunately, the numbers of cats studied was small, the specific diseases were not

defined, and there was no control group. However, in the absence of clear evidence, and in light of their safety, consideration should be given to B12 assays in the initial evaluation of dogs and cats with chronic intestinal disease, and parenteral administration during the initial management of IBD if low serum cobalamin is identified. Dogs and cats are typically supplemented with B12 at a dose of 250 µg (cats) or 500 µg (dogs) per dose, subcutaneously or intramuscularly, weekly for 4 to 5 weeks (Simpson, Fyfe et al. 2001). No study has yet evaluated the clinical response to folate supplementation in dogs or cats with chronic intestinal disease.

Vitamin K. Vitamin K deficiency leading to coagulopathy and clinically recognizable hemorrhage has been reported to occur commonly in cats in association with IBD and may also occur in dogs (Center, Warner et al. 2000). Coagulation tests normalized in all the cats reported that were treated with parenteral vitamin K1 (2.5–5 mg per cat, repeated two or three times at 12-hour intervals). All affected cats had severe IBD, and some had concurrent cholangiohepatitis.

Antioxidants. In human patients with ulcerative colitis (UC) or Crohn's disease (CD), deficiencies in zinc and vitamins A, E, B6, thiamine, and riboflavin have also been described and may contribute to mucosal oxidative damage, anemia, increased intestinal permeability, and persistent inflammation. A recent study assessed the plasma antioxidant status and proinflammatory cytokines of 26 CD patients. Decreased selenium concentrations and erythrocyte glutathione peroxidase activity were found in these patients. In addition, glutathione peroxidase activity was inversely correlated with plasma TNF-α concentrations, and serum selenium was inversely correlated with plasma levels of both TNF-α and the soluble receptor of IL-2 (Reimund, Hirth et al. 2000). It is likely that similar deficiencies occur in severely affected feline and canine patients, and consideration of parenteral fat-soluble vitamin administration is warranted in severely malnourished cases.

Zinc. The possibility that zinc deficiency might coexist in patients with IBD bears special consideration since zinc deficiency exacerbates diarrhea in humans and rodents. Oral supplementation improves histological recovery, normalizes absorption, and decreases NF-κB nuclear binding in experimental models of diarrhea (Altaf, Perveen et al. 2002). In a study of CD patients with increased intestinal permeability, daily oral zinc supplementation improved symptoms and normalized the permeability in 80% of cases (Sturniolo, Di et al. 2001). Additional mechanisms for the effect of zinc treatment on the duration of diarrhea include improved absorption of water and electrolytes, increased levels of brush border enzymes, and faster regeneration of the intestinal epithelium.

Potential Role of Dietary Antigens in the Pathogenesis of Inflammatory Bowel Disease

As stated, exaggerated responses to dietary antigens are often suspected in canine and feline IBD. Elimination diets have proved to be effective in dogs and cats with small and large intestinal lymphocytic-plasmacytic, eosinophilic, and mixed cellular infiltrates (Guilford, Jones et al. 2001; Nelson, Dimperio et al. 1984; Nelson, Stookey et al. 1988; Hirt and Iben 1998). In a study of 16 feline cases of elimination-challenge proven dietary hypersensitivity with chronic gastrointestinal signs, all 16 cats had mild to severe inflammatory infiltrates in at least one region of the bowel (Guilford, Jones et al. 2001). The infiltrates were lymphocytic, lymphocytic-plasmacytic (most cases), or eosinophilic (two cases). All cases responded completely to the elimination diet alone and offending foods were identified in all cases. In a report of 13 dogs with lymphocytic-plasmacytic colitis, clinical signs resolved in all 13 with the introduction of an elimination diet, and of 11 dogs rechallenged with their original diet, nine relapsed (Nelson, Stookey et al. 1988). In a further report of six cats with lymphocytic-plasmacytic colitis, all six responded completely to an elimination diet (Nelson, Dimperio et al. 1984). A complete clinical response to an elimination diet has been reported in a cat with duodenal and ileal lymphocytic infiltrates so severe that a histological diagnosis of intestinal lymphosarcoma was made (Wasmer, Willard et al. 1995).

The theoretical basis for the use of protein hydrolysate diets in IBD is that a reduction in immunogenic epitopes being presented to the mucosal immune system while dysregulation is present will increase the potential for resolution. Thus the argument for the use of a hydrolysate diet is independent of whether a dietary specific immunological response is suspected to be present or not. Experience with protein hydrolysate diets is increasing, and anecdotally they appear to be very effective adjuncts to pharmacological therapy, even as sole therapy. Clinical resolution with histological improvement has been reported in four of six dogs with refractory IBD when treated with a hydrolyzed soy-protein diet alone (Marks, Laflamme et al. 2002). A similar study of dogs with IBD documented equally beneficial results utilizing a different hydrolyzed soy protein diet (V. Biourge, personal communication).

Although small and uncontrolled, these results are encouraging, since five cases in the first study had

previously failed elimination diet trials. However, it is possible that nutritional factors other than protein hydrolysis are responsible. These could include dietary digestibility, correction of vitamin or mineral deficiencies, and a lowered n-6:n-3 fatty acid ratio, and the potential for an immunomodulatory effect of soy isoflavones within the diet.

One could argue that IBD should not be "diagnosed" if there is a complete response to dietary therapy alone and that a diagnosis of dietary intolerance should be made. However, this is probably more semantic than helpful, since it is equally possible that eliminating the quantitatively most significant antigen source is sufficient to eliminate clinical signs, reduce inflammation, and allow restoration of normal mucosal immunity, even if dietary hypersensitivity is not the primary pathogenic process.

Nutritional Strategies for Therapy of Inflammatory Bowel Disease

Pre- and Probiotics. It is increasingly clear that dietary influences on the intestinal flora are involved in health and disease. On heating, the amino acid lysine reacts with reducing sugars to form Maillard compounds that cannot be digested or absorbed in a usable form (Larsen, Calvert et al. 2002). This serves as substrate for luminal bacteria in the small intestine, leading to quantitative and/or qualitative changes in the flora. This leads to increased bile acid deconjugation and loss of the bile acid conjugate taurine, thus increasing the dietary requirement for taurine in canned compared with dry diets. This effect is reversible with antibiotics (Kim, Rogers et al. 1996). Additionally, fermentable fiber has been shown to profoundly affect intestinal flora, in addition to its effect on enterocytes, by promoting the development of beneficial species (see above) (Bamba, Kanauchi et al. 2002). This prebiotic effect reduces or prevents inflammation in experimental models of IBD (Guarner, Casellas et al. 2002; Kanauchi, Suga et al. 2002). Therefore, a fermentable fiber source should probably be included as part of dietary therapy, although information regarding which (e.g., resistant starch, fructosoligosaccharides, inulin) and how much is lacking. The addition of fructosoligosaccharides (FOSs) to feline diets at 0.75% DM did not affect duodenal flora but it did increase the numbers of lactobacilli and reduce the numbers of *E. coli* in the fecal flora of healthy cats (Sparkes, Papasouliotis et al. 1998a, 1998b). Healthy German Shepherd dogs believed to have bacterial overgrowth were supplemented with FOSs at 1.0% of their diet as fed (Willard, Simpson et al. 1994). Changes were recognized in the duodenal bacterial flora but these changes were of less magnitude than seen in normal dogs for these parameters. The clinical significance of these studies in cats and dogs with IBD is unknown.

A probiotic has been defined as "a preparation containing viable, defined micro-organisms in sufficient numbers, which alter the established intestinal microflora by implantation or colonization in a compartment of the host, and by that exert beneficial health effects in the host" (Schrezenmeir and de Vrese 2001). Unfortunately, most commercial veterinary probiotic preparations are not accurately represented by label claims, reflecting the poor quality control for most commercial veterinary probiotics (Weese and Arroyo 2003).

Much work is required to define what constitutes optimal numbers and species of intestinal micro-organisms. However, it is likely that through interaction with the gut flora, certain diets could protect against IBD, while others could actually predispose to the development of IBD. Until further data are available, it is prudent to select diets with a high digestibility in the management of IBD though with a source of fermentable fiber. An avoidance of canned diets in feline cases seems rational at present.

Glutamine. It has been proposed that gut mucosal turnover and barrier function is compromised during IBD due, in part, to a relative glutamine deficiency. This is supported by experimental studies that have demonstrated a reduction in mucosal inflammation and lipid peroxidation products following luminal glutamine supplementation in models of mucosal inflammation (Kaya, Gur et al. 1999). Caution should be heeded in interpreting many of the experimental studies, as disparate dietary effects are often seen. It is clear that the availability of glutamine is probably beneficial in all causes of acute and chronic enteritis. However, it is uncertain if any benefit will be provided by supplementation beyond that present in adequate amounts of intact protein. Studies of spontaneous IBD in human patients have yet to provide any evidence that "extra" glutamine provides any benefit over conventional levels (Goh and O'Morain 2003). This finding is consistent with the previously discussed finding that glutamine supplementation beyond that provided by intact dietary protein has no further benefit in acute gastrointestinal disease.

Arginine and Nitric Oxide. The main potential mechanism for the positive action of luminal arginine supplementation in IBD is via modulation of nitric oxide (NO) production within the mucosa. In the past 10 years, it has become clear that NO is an important molecule in normal intestinal homeostasis and in the inflamed intestine. Numerous studies have attempted to elucidate whether NO production during intestinal inflammation is beneficial or

deleterious, producing conclusions that range from bad through indifferent to essential (Perner and Rask-Madsen 1999). Nitric oxide is produced in low amounts constitutively by endothelial and neuronal nitric oxide synthases (eNOS and nNOS). During inflammation, and under the transcriptional control of NF-κB, a third NO synthase enzyme is induced (iNOS) in most activated leukocytes and activated epithelial cells, which produce much greater amounts of NO than produced constitutively (Grisham, Pavlick et al. 2002). Recently it has been reported that iNOS is expressed in canine IBD, and that NO-derived nitrite is increased in the colonic lumen of affected dogs (Gunawardana, Jergens et al. 1997; Jergens, Carpenter et al. 1998).

Constitutively produced NO serves to maintain intestinal perfusion, inhibit longitudinal smooth muscle contraction, inhibit the expression of broad-spectrum endothelial adhesion molecules, coordinate epithelial cell turnover, and promote barrier integrity (Perner and Rask-Madsen 1999). In large iNOS-dependent quantities, studies have shown that NO can scavenge free radicals, preserve epithelial integrity or promote epithelial apoptosis with loss of barrier integrity and increased bacterial translocation, induce or inhibit inflammatory cytokines, and lead to irreversible host-protein nitrosylation and dysfunction (Pavlick, Laroux, et al. 2002). Variables that affect the role of NO include the cellular source, timing of production in relation to the insult, chronicity of the disease, quantity produced, and the presence of superoxide leading to the formation of peroxynitrite. It is not surprising then that such a heterogenous collection of responses under different experimental and clinical settings has lead to controversy about whether inhibition of iNOS in IBD might be beneficial or detrimental. Importantly, most experimental models of intestinal inflammation mimic human forms of IBD and probably do not reflect the same pathogenesis as that seen in feline and canine IBD. Further research, specific to feline and canine disease, needs to be performed before the use of iNOS inhibitors or even NO-donors or precursors could be recommended therapeutically.

Antioxidants. Increased free radical production is a cardinal characteristic of almost any inflammatory disease and has been demonstrated convincingly in human IBD patients. In addition, as previously stated, deficiencies in vitamins and minerals associated with oxidant defense (vitamins A, E, C; Zn, Mn, Cu) are commonly associated with IBD, and their supplementation has been shown to be effective in reducing the effects of intestinal damage following experimental insults. Although it is expected that oxidative stress is a feature of canine and feline IBD, the absence of significant numbers of the major oxidant producing species (neutrophils and macrophages) in the majority of intestinal infiltrates suggests it is less significant than in its human analogs. Nonetheless, supplementation of dietary antioxidants seems prudent until reasons are provided to suggest their lack of efficacy or detrimental effects. It is currently unknown what the optimal dose and combination of antioxidants are for patients with IBD.

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 (Meyer, Elashoff et al. 1994; Lin, Doty et al. 1990), 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 (Poley and Hofmann 1976). Fat malassimilation can also be associated with malabsorption of bile acids, resulting in deconjugation of unabsorbed bile acids and increased mucosal permeability and secretion (Cummings, Wiggins et al. 1978). Dietary fat restriction is particularly important in patients diagnosed with lymphangiectasia, with many patients needing restriction to less than 15% fat kJs or kcals. Unfortunately, there are few commercial veterinary diets available that contain less than 15% fat kJs or kcals. It is the author's opinion that when severe lymphangiectasia accompanies IBD, priority should be given to the feeding of a restricted fat diet over antigenic novelty. Further studies are warranted to document the touted benefits of medium-chain triglycerides (MCTs), as increasing evidence has highlighted their limitations based on high cost, low palatability, and evidence that at least in the dog, absorption still occurs via intestinal lymph (Jensen, McGarvey et al. 1994).

It is becoming increasingly clear that the significance of fat malabsorption is far less in cats with chronic intestinal disease than dogs. A recent study evaluated 60 cats with chronic, nonspecific diarrhea of at least 1 month's duration (Laflamme, Xu et al. 2011). They were fed either a high-fat [23.2% dry matter basis (DMB)] or a low-fat (10.5% DMB) diet for 6 weeks. Improvement in fecal consistency was seen in most cats in both groups, and there was no difference in rates or degrees of improvement between groups. It is likely that affected cats either had an adverse reaction to food, or idiopathic inflammatory bowel disease, or both, consistent with the prevalence previously described (Guilford, Jones et al. 2001). Thus this study

emphasized the important role of dietary manipulation in chronic intestinal disease, and the lack of importance, at least in that study population, of dietary fat restriction in cats with chronic diarrhea.

Polyunsaturated n-3 fatty acids. Dietary polyunsaturated fatty acids (PUFAs) can modulate immunity via several mechanisms (Calder and Grimble 2002; Lee, Plakidas et al. 2003; Weatherill, Lee et al. 2005; Calder, Bond et al. 1990; Kearns, Hayek et al. 1999; Dooper, Wassink et al. 2002; Geyeregger, Zeyda et al. 2005). The dietary content of PUFAs determines the proportions of the n-6 and n-3 PUFAs incorporated into leukocyte cell membrane phospholipids. The n-3 PUFA eicosapentaenoic acid (EPA) competes with the n-6 arachidonate (AA) as a substrate for cyclooxygenase (COX) and lipoxygenase (LOX) after cleavage from the cell membrane, and the dietary proportions of n-6 and n-3 PUFAs determine if the prostaglandins, thromboxanes, leukotrienes, and platelet activating factor (eicosanoids) are produced from EPA or AA. EPA is a less efficient substrate for COX, resulting in reduced prostaglandin production. Eicosanoids produced from EPA range from antagonistic to equipotent to those derived from AA, and the overall effect on immunity is not explained simply by the reduced efficacy of EPA-derived eicosanoids. The effects and mechanisms of modulation of eicosanoids by dietary lipid is complex, although there is some value to the generalization that diets enriched in n-3 PUFAs will reduce inflammation relative to diets enriched in n-6 PUFAs.

PUFAs also directly affect gene transcription through the peroxisome proliferator-activated receptors (PPARs), a family of cytosolic proteins that, once bound to an appropriate ligand, diffuse into the nucleus and promote or inhibit gene transcription. PPARs are expressed by macrophages, lymphocytes, and dendritic and endothelial cells (Glass and Ogawa 2006). Activation of PPARs by EPA leads to reduced TNF-α, IL-6, and IL-1 production by macrophages, and reduced IL-2 production by lymphocytes (Kliewer, Sundset et al. 1997; Glass and Ogawa 2006; Kostadinova, Wahli et al. 2005).

The incorporation of EPA in place of AA in phospholipid membranes of lymphocytes affects the function of the lipid rafts within which T-cell receptors (TCRs) are localized. This decreases signal transduction through the TCR reducing T-cell activation (Geyeregger, Zeyda et al. 2005). Lastly, both EPA and docosahexaenoic acid (DHA) antagonize the interaction between gram negative lipopolysaccharide (LPS or endotoxin) and Toll-like receptors, reducing the production of COX, TNF-α, IL-1, IL-6, and IL-8, and improving morbidity in severe sepsis (Weatherill, Lee et al. 2005; Mayer, Meyer et al. 2003; Lee, Zhao et al. 2004).

Predicting the effect of PUFAs within a diet has to take into account (a) the total fat content, (b) the relative proportions of 18-carbon and 20-carbon n-3 and n-6 PUFAs, (c) the absolute amounts of all individual n-3 and n-6 PUFAs, (d) the previous dietary history of the animal, and (e) the duration of exposure to the diet in question. Describing the fat content of a diet by a simple ratio of n-6 to n-3 PUFA provides very limited and potentially misleading information. In addition, supplementation of a diet with a source of n-3 PUFA (e.g., marine fish oil) will have varying effects depending on the diet and patient. Most commercial diets are highly concentrated in n-6 PUFAs, and the addition of a small amount of n-3 PUFAs will achieve little.

Where information on specific dietary fatty acid concentrations is not available, a ratio of total n-6 to n-3 of less than 5 may be effective for reducing pruritis in atopic dermatitis, whereas a ratio less than 3.5 : 1 may be needed for more serious inflammatory diseases, and ratios as low as 1.3 : 1 may be optimal (Bauer 2007; LeBlanc, Dietrich et al. 2007; LeBlanc, Horohov et al. 2008; Saker, Eddy et al. 1998). The exact amount of fish oil required to be added depends on the basal diet.

A class of transcription factors that may have an important role in IBD is the PPARs. Upon binding with their ligand, PPARs dimerize with the RXR co-receptor, then translocate to the nucleus and bind to PPAR-response elements. Although the understanding of the range of action of PPARs and their ligands in cats and dogs is rudimentary, it is interesting to note that NF-κB-dependent gene transcription is decreased by PPAR-γ ligands. Indeed, it has been shown that PPAR-γ ligands can potently inhibit NF-κB-dependent cytokine production by the murine colonic epithelium and significantly decrease intestinal inflammation in an experimental model of IBD (Takagi, Naito et al. 2002). This is especially interesting given that certain n-3 fatty acids are known PPAR-γ ligands (Kliewer, Sundseth et al. 1997).

Lastly, although as yet unproven, aberrant immunological responses to enteric flora are considered a key component to the dysregulation of immunity in feline and canine IBD (Burgener, Konig et al. 2008). If this is the case, the recent finding that n-3 PUFAs are capable of acting as competitive agonists of the bacterial LPS receptor complex (Toll-like receptor 4) is another potential mechanism by which these PUFAs could be beneficial in IBD (Lee, Plakidas et al. 2003).

Fish oil supplementation has been reported to be beneficial in ulcerative colitis and Crohn's disease patients, but

the results are controversial. One study of 18 patients with ulcerative colitis demonstrated a reduction in the number of CD3 positive cells within the intestinal mucosa, reduced expression of MHC II antigens, and reduced plasma cell numbers following treatment with fish oil extract compared with placebo (Almallah, Richardson et al. 1998). 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 EPA daily, despite a significant reduction in LTB_4 synthesis by blood peripheral neutrophils (Hawthorne, Daneshmend et al. 1992).

The differences between the reports regarding study design, supplement composition, dose, whole diet n-6 : n-3 ratios, and assessment of clinical improvement may in part explain the conflicting results. One study compared the efficacy of fish oil to sulfasalazine in the treatment of mild to moderate active ulcerative colitis in humans (Dichi, Frenhane et al. 2000). Treatment with fish oil resulted in greater disease activity as detected by a significant increase in platelet count, erythrocyte sedimentation rate, C-reactive protein, and total fecal nitrogen excretion. Often overlooked is the increase in lipid peroxidation after fish oil supplementation is instituted (Girelli, Olivieri et al. 1994). Antioxidant supplementation may be able to counteract the potentially adverse effects of n-3 fatty acids. Most of the literature regarding n-3 fatty acid administration fails to address the amount of attendant antioxidant supplementation. There are no reports in the veterinary literature demonstrating the efficacy of n-3 fatty acid supplementation in managing canine or feline IBD. Studies in healthy dogs fed a diet with an n-6 to n-3 ratio of 1.4 : 1, demonstrated a decreased production of PGE2 by stimulated peripheral blood mononuclear cells, and a decreased delayed type hypersensitivity response, compared to dogs fed a diet with a ratio of 5.4 : 1 (Wander et al. 1997). Increases in certain long-chain n-3 fatty acids and decreases in arachadonic acid were identified in the small intestine and colonic mucosa of healthy Beagles fed the same ratios (Reinhart and Vaughn 1995). There is insufficient evidence to make firm recommendations for disease modulation in cats using dietary PUFAs. Using a dietary fat content of approximately 70 g/kg DMB, Saker and colleagues found that a total n-6 to n-3 ratio of 1.3 : 1 (using corn oil, animal fat, and menhaden fish oil) reduced platelet aggregation (Saker, Eddy et al. 1998). Such a value provides a very rough estimate to the proportions required for modulating eicosanoid production, although the concentrations of EPA and AA were not specifically assayed. In addition, the dietary concentrations required for the other effects of n-3 PUFAs are unknown. Further research is necessary to determine the clinical benefits in dogs and cats with IBD and currently no effective, established dosages exist.

Recommendations

The optimal nutritional approach for dogs and cats with IBD remains to be determined and certainly varies from animal to animal. Although there are several mechanisms by which diet can affect the progression, maintenance, or resolution of chronic mucosal inflammation, it is undetermined how important any individual component is. Nonetheless, proper dietary management can result in decreased utilization or dosage of pharmacologic therapy and in some cases can lead to clinical resolution as a sole therapy.

The current recommended management following diagnosis is as follows:

1. Assess the nutritional status of the patient. This will include physical parameters such as body condition, lean body mass, history of recent weight loss, current appetite, hydration, presence of edema, and coat condition. Clinicopathological indices include serum albumin concentration, serum electrolyte concentrations, erythrocyte and leukocyte indicators of malnutrition, evidence of protein-losing gastroenteritis (PLGE) (panhypoproteinemia, hypocholesterolemia, lymphopenia), serum PIVKA measurement (proteins invoked by vitamin K antagonism) or coagulation panel to assess vitamin K status, serum vitamin B12 concentration, and folate.
2. Address specific concerns regarding malnutrition. This may include vitamin B12, folate, or vitamin K1 supplementation.
3. Address anorexia through pharmacological means (i.e., specific therapy for IBD) and consider supplemental or supportive nutrition in severely malnourished individuals. Indicators for the need for supportive nutrition would include persistent anorexia, recent weight loss of >10% body weight, anemia, hypoalbuminemia, and a body condition score of 3 or less on a 9-point scale with poor appetite.
4. Select a highly digestible, novel protein or hydrolyzed protein diet and feed exclusively until immunosuppressive therapy can be discontinued.
5. Consider fat restriction in severe cases, or where there is histological evidence of lymphangiectasia.
6. If dietary fat is not limiting, then consider enrichment of the diet with n-3 PUFAs using fish oil to achieve a crude ratio of <2 : 1, n-6 : n-3.

Protein-Losing Enteropathies

Increased lymphatic flow as the result of mucosal inflammation is expected, and dilation of intestinal lacteals is a common finding on histopathology (Wilcock 1992). Lymphatic obstruction from extraluminal fibroplasia and constriction, intraluminal adhesions, and debris can lead to a net loss of intestinal lymph. Panhypoproteinemia and hypocholesterolemia, with or without lymphopenia, suggest loss of intestinal lymph. A concern in managing lymphangiectasia is in prioritizing dietary therapy, since in many cases, chronic intestinal inflammation accompanies the lymphatic obstruction (Kull, Hess et al. 2001). Many select protein or hydrolyzed protein diets suitable for the management of IBD contain higher fat contents than would be ideal for severe lymphangiectasia. As stated above, when severe lymphangiectasia accompanies IBD, priority should be given to the feeding of a restricted fat diet over antigenic novelty, since the hypoproteinemia is often the most life-threatening derangement. Reducing dietary fat decreases lymphatic flow, reduces lacteal dilation and pressure and hence limits lymphatic protein loss (Olson and Zimmer 1978). Practically, this means the selection of diets that provide <20% of kJs or kcals as fat, of which there are currently few commercial diets. The reduced lymphatic pressures reduce protein loss and can lead to normalization of serum protein concentrations (Olson and Zimmer 1978). Addition to the diet of medium-chain triglycerides cannot be recommended given their high cost, low palatability, and evidence that at least in the dog some absorption still occurs via intestinal lymph (Jensen, McGarvey et al. 1994).

In severe cases, there is sufficient disruption of the mucosa that marked malabsorption accompanies the enteric protein loss. In those cases, semi-elemental or even elemental diets may be required. There are currently no veterinary elemental diets, and no ideal human formulas. Commercial human formulas may be excessive in fat, of too high an osmolarity, contain lactose, be too low in amino acids, and/or be deficient in one or more vitamins or minerals. In this author's practice, a human elemental diet can be supplemented with a lactose-free whey protein isolate, multivitamins and minerals, and canola oil (as a source of linoleic and α-linolenic acid) for use in canine and feline patients (see Table 12.5).

Table 12.5. Balanced Fat-Restricted Elemental Diet Suitable for Canine and Feline Patients

Ingredient	Amount
*Elemental 028®	100 g
Centrum® A to Z Multivitamin tablets	¼ tablet
Canola oil	1 mL
Whey protein isolate	20 g
Taurine (for cats)	50 mg
Total metabolizable energy (ME): 416 kcal (1740 kJ)	
ME density: 3.4 (14.2 kJ) kcal/g (DMB)	
Nutrient composition (% of ME):	
Digestible protein	25 %
Fat	16 %
Carbohydrate and ash	59 %

*SHS International Ltd., Liverpool, United Kingdom

Adverse Food Reactions and Food Responsive Diarrhea

Cases of gastrointestinal disease that respond completely to appropriate dietary management and that have no histological evidence of enteritis or morphological changes, have been referred to as cases of food responsive diarrhea (German, Hall et al. 2001). In practice, cats and dogs that present with chronic vomiting and/or diarrhea will usually be subjected to an elimination dietary trial prior to the collection of intestinal biopsies. Therefore, when vomiting or diarrhea resolves on an elimination trial and no intestinal biopsies have been taken, the disease could be dietary hypersensitivity, dietary intolerance, or mild IBD. In those cases, the terms "food responsive diarrhea," or "adverse food reaction" are appropriate. However, there are some circumstances that lead to procurement of intestinal biopsies prior to a dietary trial, which in some cases can produce unremarkable histological findings. In those cases, an adverse reaction to food cannot and should not be excluded.

The ideal diagnostic and long-term diets for patients with adverse food reactions are based mostly on protein novelty, or protein hydrolysis. However, other mechanisms than the immunological responses to dietary antigens are probably more important when no inflammatory mucosal infiltrate is present. In a study of 55 cats with chronic vomiting and/or diarrhea, 16 cats were diagnosed as having food sensitivity based on elimination-challenge trials (Guilford, Jones et al. 2001). However, a further 11 cats responded completely to an elimination diet, but did not recrudesce during a challenge trial. Similar to the food sensitive cats, the non-food-sensitive cats had a range of histopathological changes from none to moderate lymphocytic-plasmacytic enteritis.

Table 12.6. Potential Mechanisms for Non-immunological Adverse Food Reactions

Factor	Mechanism
Digestibility	Poorly digestible nutrients leading to bacterial fermentation, osmotic diarrhea, etc.
Lactase deficiency	Undigested lactose leading to fermentation and osmotic diarrhea
Nutrient deficiency	For example, zinc, B12 leading to mucosal dysfunction
Fiber	Fiber-responsive diarrhea—promotion of water resorption, restored motility, prebiosis, increased fecal bulk, passage of hairballs
Food additives	Idiosyncratic, pharmacological

Recommendations

It is clear then that a large number of dogs and cats with chronic idiopathic gastrointestinal disease will respond completely to dietary manipulation. In the absence of a specific protein hypersensitivity, the mechanisms remain obscure. Possible mechanisms are listed in Table 12.6. However, ignorance of underlying mechanisms further increases the desire to manage such cases with highly digestible diets that contain as few ingredients as possible. The same general approach to the dietary choices for acute gastroenteritis is probably suitable for such cases.

Short Bowel Syndrome

Short bowel syndrome (SBS) is used to describe the nutritional and metabolic sequelae that accompany resection of sufficient small intestine to cause clinically significant malabsorption and malnutrition. Neoplasia, intussusception, linear foreign bodies, trauma, infarction, and mesenteric torsion are all diseases that may require massive intestinal resection. Resection of at least 70% of the small intestine is required to induce short bowel syndrome (Yanoff, Willard et al. 1992). In addition, the terminal ileum and ileocolic (IC) valve are of great physiological value, and animals will perform much poorer even with only 50% resections if they are removed (Joy and Patterson 1978).

Pathophysiology

Following large-scale resection, postprandial motility is altered such that gastric emptying is delayed, and intestinal transit times are increased across the remaining portions (Johnson, Sama et al. 1996). The modification of motility appears to be an important part of the compensation for the loss of intestinal mass. Nonetheless, compensation through altered motility may be inadequate in the face of massive resection, such that artificially increasing intestinal transit times by inducing periods of retrograde movement of ingesta in portions of small intestine can lead to significantly increased absorption and clinical improvement (Gladen and Kelly 1980). These findings emphasize the importance of mixing and retaining ingesta in the remaining portion of the intestine and highlight problems that accompany overfeeding at any one meal.

Loss of the absorptive area results in the inability to sustain adequate absorption of water, electrolytes, and other essential nutrients when fed conventional diets. Simple compensation through increased intake may be sufficient in mildly affected cases, but the majority require significant dietary adjustment. Dehydration, generalized protein-calorie malnutrition, and multiple nutrient deficiencies can result. Initial clinical signs include vomiting, diarrhea, and rapid weight loss (Yanoff, Willard et al. 1992; Johnson, Sama et al. 1996).

The active uptake of bile acids occurs in the ileum and is mediated by a sodium-dependent bile acid transporter in the brush border membranes. Similarly, the enterocyte membrane receptor for the B12-intrinsic factor complex is expressed in the terminal ileum (Levine, Allen et al. 1984). Therefore, loss of the ileum leads to bile acid and vitamin B12 malabsorption.

Intestinal Adaptation

Through the mechanisms discussed above (intestinal recovery and adaptation), the presence of luminal nutrients stimulates the remaining small intestine to undergo a period of hypertrophy and hyperplasia, which may continue for several weeks. The colon also becomes an important digestive organ in patients with SBS (Jeppesen and Mortensen et al. 1998). Sodium, water, and some amino acids are absorbed in the colon, as well as energy from absorbed short-chain fatty acids. Thus, a source of readily fermentable fiber should be included in all diets, while insoluble nonfermentable fiber should be kept to a minimum, to maximize nutrient digestibility (Roth, Frankel et al. 1995).

Feeding Recommendations

Dietary management is complex and needs to be individualized for each patient on the basis of the residual intestine, nutritional state, current diet, underlying disease, and the client's lifestyle limitations. In addition to nutrient intake, management of SBS also requires appropriate oral

rehydration, vitamin and mineral supplementation, and pharmacotherapy. Several medications provide a useful adjunctive function to dietary intervention, including antidiarrheal agents, H2 antagonists and proton pump inhibitors, pancreatic enzymes, and antibiotics. Future therapy will likely involve direct stimulation of intestinal adaptation through the administration of trophic factors such as GLP-2. The following list provides guidelines:

1. *Resection of jejunum with intact duodenum, IC valve, and colon.* Feeding multiple small meals will improve absorption and decrease episodes of vomiting. Clinical improvements have been seen in the author's practice by increasing the frequency of feeding up to six times daily in some cases. Evenly spacing meals as much as is possible will also help. As with most intestinal diseases, diets with high digestibilities for fat, protein, and digestible carbohydrate should be preferred.

   Fat is probably the limiting nutrient in absorption, and fat malabsorption likely exacerbates the diarrhea or vomiting of most cases. Avoidance of high-fat diets is recommended, although it is not known how restricted fat should be, and individualization is stressed. An empirical recommendation is to feed less than 25% of ME as fat, and reducing intake further if diarrhea or vomiting continues.

   Dietary fiber is important to stimulate intestinal adaptation, maximize colonic absorption, and bind unabsorbed bile acids. However, excessive fiber will decrease diet digestibility, impair nutrient absorption, and exacerbate diarrhea. Psyllium and wheat bran have been shown to effectively bind bile acids, while guar gum is less effective, and cellulose is ineffective (Ebihara and Schneeman 1989; Floren and Nilsson 1987; Ryden and Robertson 1997; Buhman, Furumoto et al. 1998). The addition to the diet of 5% psyllium or wheat bran on a dry matter basis is reasonable, depending on the fiber content of the chosen diet, but improvements have been seen in the author's practice with the addition of up to 10% DMB. Commercial high-fiber diets containing predominantly cellulose are not recommended. Any introduction or increase of fiber should be gradual over 3 to 5 days. Immediately after intestinal resection, water and electrolyte balances should be carefully monitored. Serum B12, folate, and taurine should be intermittently monitored after 2 to 4 weeks.

   Hydrolyzed protein diets may be beneficial, although protein digestion and absorption is not thought to be limiting in most patients. In addition, currently available hydrolysate diets may not be restricted enough in their fat content for severely affected patients (Cave 2006).
2. *Greater than 50% resection of the small intestine with partial resection of ileum.* Bile salt-induced diarrhea is common and may not be adequately controlled through dietary fiber. If 5% (DMB) psyllium or wheat bran is insufficient in controlling diarrhea, administration of cholestyramine 100–300 mg/kg PO q 12 h is recommended to bind bile salts left unabsorbed by the resected ileum. Supplemental taurine is advised in both cats and dogs with long-term cholestyramine treatment. Vitamin B12 absorption should be measured and, if low, the patient should be replenished by injecting vitamin B12, 250 µg (cats) or 500 µg (dogs) per dose, subcutaneously or intramuscularly, weekly for 4 to 5 weeks, then every 1 to 4 weeks as indicated.
3. *Complete resection of ileum.* Fat restriction is mandatory. Diets with less than 25% ME fat are indicated, and home-prepared diets formulated by a veterinary nutritionist may be required. With the larger resection, the bile acid pool can become depleted, and cholestyramine may not be beneficial. Parenteral vitamin B12 replacement and taurine (500 mg per day) supplementation is required.
4. *Massive (>70%) resection of jejunum and ileum.* Total parenteral nutrition or partial peripheral nutrition may be initially required. However, a delay in the introduction of enteral nutrition can limit the degree of intestinal adaptation. Initial oral feeding does not need to meet the nutritional requirement of the patient if parenteral nutrition is supplied, and as little as 25% of the patient's RER can be fed over several meals. After the initial period of parenteral nutrition, a concerted attempt should be made to wean patients to an oral diet as soon as possible. An elemental diet may be required, although fiber supplementation is still likely to be beneficial, and careful attention to nutrient deficiency is still necessary (see above).

LARGE INTESTINAL DISEASE

Colitis

Acute Colitis

Ingestion and colonic passage of indigestible material is probably the most common cause of acute colitis; bone fragments, fabric, food packaging, and plant material are frequently incriminated in the author's experience. Other causes include infectious agents such as *Trichuris* spp., *Giardia* spp., and possibly bacterial pathogens such as *Campylobacter* spp., and *Clostridium difficile* and *Clostridium perfringens*. In many cases, the original insult has

resolved or been passed by the time of presentation. As such, most cases resolve without specific diagnosis or management.

When colitis is present, there is an increase in the number of giant migrating peristaltic waves, while segmental contractions are decreased or even absent (Sethi and Sarna 1991). The absence of segmental contraction leads to frequent defecation following colonic peristalsis and produces urgency to defecate in the patient. A single colonic insult can result in prolonged disturbances of motility that can last 2 to 3 weeks, despite histological resolution of inflammation (Sethi and Sarna 1991).

Normally in response to a meal there is an increase in segmental contractions along the colon, both immediately and several hours after a meal when ingesta enter the colon. Giant migrating contractions occur rarely in the first 8 hours following a meal (Sarna and Lang 1989). When the colon is inflamed, that postprandial increase in segmental contractions does not occur, but instead feeding further increases the giant migrating waves that are increased by the inflammation (Sethi and Sarna 1991). The entry of ingesta into the inflamed colon during the late postprandial period stimulates an excessive number of giant migrating contractions. These peristaltic waves may be associated with postprandial abdominal discomfort and contribute to an increased frequency of defecation.

There are no published studies that have evaluated different dietary compositions for the management of acute colitis in dogs or cats. In light of the known effects of luminal ingesta on signs of colitis (e.g., diarrhea, urgency to defecate, abdominal discomfort), it seems prudent to recommend feeding a diet that results in the least possible amount of ingesta to be passed into the colon. Such a diet would be referred to as "low residue." Highly digestible diets formulated for small intestinal disease would therefore qualify. Avoiding high-fat diets may be warranted because of the effect of unabsorbed fatty acids on the colonic mucosa (see above). However, the caloric density and digestibility of fat allows feeding smaller meals with lower residue. In addition, the presence of fat in the jejunum slows ileocolonic transit times in humans (Hammer, Hammer et al. 1998). Lastly, in cats, dietary fat restriction has not been shown to be beneficial (Laflamme, Xu et al. 2011).

In direct contrast to the argument for highly digestible diets to be fed to patients with acute colitis is the observation that dietary fiber may be of benefit in many cases. The effect of dietary fiber in the colon has been discussed above. Fibers with differing degrees of fermentability produce different clinical effects. Variables that affect the response to dietary fiber in any patient include, but are not limited to, existing colonic microflora, colonic motility, disease type, disease severity and heterogeneity along the colon, and background diet. At present, the interaction between differing fiber types and different diseases is not understood, nor is the disease in affected patients completely understood in most cases. For those reasons, it seems prudent when adding dietary fiber to recommend the empirical use of mixed fermentable sources such as psyllium husk, and if the condition is poorly responsive, to try more fermentable sources such as hydrolyzed guar gum. When selecting commercial diets in cases of acute colitis, most commercial fiber sources could be considered to be mixed sources (e.g., pea hulls, soy fiber, rice bran) and would likely qualify empirically. There is still much to learn.

Chronic Colitis

Dietary requirements for chronic colitis are similar to those for acute colitis, namely the contrasting features of high digestibility to limit the passage of ingesta into the colon, and the provision of adequate dietary fiber. As for acute colitis, the ideal fiber quantity and type is not known, and likely differs between patients. Butyrate enemas have been shown to reduce inflammation and symptoms in humans suffering from Crohn's disease or ulcerative colitis, demonstrating the need for some fermentable fiber to be present (Luhrs, Gerke et al. 2002; Breuer, Soergel et al. 1997; Patz, Jacobsohn et al. 1996). Additional benefits of nonfermentable fiber include adsorption of colonic bile acids and other mucosal irritants and the symptomatic improvement of fecal consistency.

In chronic colitis, the role of dietary antigens should also be considered. As in chronic small intestinal enteropathies, aberrant immune responses to luminal dietary antigens are prominent components of the disease in many patients. Many cases of canine food hypersensitivity that produce gastrointestinal signs have signs of large intestinal disease (Paterson 1995). In a study of nine proven food-allergic dogs, eight of the dogs had histological evidence of mild to moderate lymphocytic-plasmacytic (LP) inflammation (Allenspach, Vaden et al. 2006). In that same study, when the antigens, proven to be allergens by oral challenge, were injected into the colonic mucosa during colonoscopy, 17 of 23 allergens produced visible mucosal reactions (wheal and flare). In a report of 13 dogs with LP colitis, clinical signs resolved in them all with the introduction of an elimination diet, and nine of 11 dogs rechallenged with their original diet relapsed (Nelson, Stookey et al. 1988). In a further report of six cats with LP colitis, all responded completely to an elimination diet (Nelson, Dimperio et al. 1984). Thus, aberrant (hypersensitive)

immune responses to dietary antigens commonly affect the colon, whether or not signs of colonic disease are present. Conversely, when signs of chronic colitis are present, food hypersensitivity should be considered.

Similarly as for chronic small intestinal inflammatory disease, the value of dietary enrichment with n-3 PUFAs for the management of chronic colitis has not been determined in dogs and cats. In the absence of evidence either way, it is reasonable to consider it as an intervention that may help. In mild cases of colonic IBD, a long-term clinical effect might occur as part of the general dietary manipulation, and in more severe cases, it may reduce the dependence on or dose of immunosuppressive therapy.

Overall recommendations for the management of chronic colitis are to firstly change to a novel or hydrolyzed protein diet. Select a diet that has highly digestible protein, fat, and carbohydrate components. Most high-quality commercial extruded diets would satisfy this requirement. If an initial response to dietary manipulation is not successful, adjust the dietary fiber content. It is currently impossible to know which animal will respond to what type and amount of dietary fiber, and empirical recommendations are misleading. Additionally, assessment of the total dietary fiber content of a selected diet is extremely difficult to do from an ingredient list, and crude fiber measurements are of limited value. Mixed fermentable sources such as psyllium can be slowly introduced up to 10% of dry matter, while highly fermentable sources such as guar gum can be slowly introduced up to 5% of dry matter. It is unlikely that a clinical response will be seen with greater amounts. Lastly, enrichment of the diet with long-chain n-3 PUFAs may help (for suggested amounts, see above).

Idiopathic Large Bowel Diarrhea

Idiopathic large bowel diarrhea is diagnosed when chronic large bowel diarrhea is present, when there is an absence of histological evidence of colitis, and when inciting causes have been eliminated (Leib 2000). Several diagnostic terms would fall under this definition including irritable bowel syndrome, colonic dysmotility, fiber-responsive diarrhea, stress-induced colitis, and nonspecific dietary sensitivity. By definition, these cases have not responded to a strict novel protein or hydrolyzed protein diet trial, but they may have idiosyncratic improvements when switched from one diet to another. In one study of 37 cases of idiopathic large bowel diarrhea, 63% responded excellently to the addition of psyllium husk powder to a highly digestible fat-restricted diet (Leib 2000). Only one case had a very poor response. The dosage used was approximately 1 g/kg/day, with a range of 0.3–4.9 g psyllium/kg per day.

Dogs with intermittently poorly formed feces that respond to a change in diet for which no mechanism is clear are referred to as being affected with nonspecific dietary sensitivity. In the majority of these cases, a clear hypersensitivity is not demonstrated. Additionally, affected dogs appear to more consistently suffer from colonic dysfunction than small intestinal dysfunction (Zentek, Hall et al. 2002). Common histological findings in the colon include reduced mucosal crypt depth, crypt widening, and increased numbers of intraepithelial T-lymphocytes (Zentek, Hall et al. 2002; Rolfe, Adams et al. 2002). Water absorption may be reduced, which is associated with reduced sodium and chloride absorption (Rolfe, Adams et al. 2002). This problem appears more common in large rather than small breed dogs. Fecal water content is likely to be decreased if dry extruded food is fed in preference to high-moisture canned diets, although overall fecal consistency is not necessarily improved in affected dogs by simply changing to a dry extruded diet (Zentek, Fricke et al. 2004). In addition, the fecal quality of some dogs may not improve with increased soluble and nonsoluble dietary fiber.

Thus idiopathic large bowel diarrhea may respond to increased dietary fiber, or it may be responsive to other dietary manipulations for reasons that are not clear. Failure to respond to one empirical dietary manipulation (e.g., the addition of fiber) should not sway the clinician away from further empirical dietary choices.

Constipation and Megacolon

Constipation can be defined as incomplete or infrequent defecation of hardened feces, often with a decreased water content and is usually associated with tenesmus. Constipation can occur as the result of excessive dehydration of the luminal contents and/or impaired motility. Dietary variables that lead to constipation have not been well defined in dogs or cats. However, ingestion of large amounts of indigestible material such as bone or wool are commonly incriminated (Nemeth, Solymosi et al. 2008). In normal humans, colonic transit time is decreased as insoluble fiber is increased, while in patients with chronic constipation, increased insoluble fiber does not speed fecal transit (Muller-Lissner 1988). Whether that reflects a cause or effect is uncertain, as is the significance to canine and feline patients. It is likely that colonic transit time partly determines the response to dietary manipulation, as it does in people (Hagiwara and Tomita 2008). However, there are no established diagnostic protocols for clearly determining colonic motility in dogs or cats and no evidence for recommending one intervention over another.

Insoluble nonfermentable fiber increases fecal bulk and increases the frequency of defecation in a normal individual. Increasing fecal bulk may exacerbate constipation in an individual with impaired colonic motility. Perhaps the poorest choice of dietary fiber in constipation is a nonfermentable, insoluble fiber that increases fecal dry matter, but not fecal water content, such as cellulose (Wichert, Schuster et al. 2002). Fiber that produces viscous gels (e.g., psyllium husk) will increase the fecal water content, in addition to increasing fecal dry matter. Short-chain fatty acids from colonic fermentation have been shown to stimulate longitudinal colonic smooth muscle contractions in kittens and adult cats *in vitro* (Rondeau, Meltzer et al. 2003). However, highly fermentable fiber may also result in the production of methane. Methane production varies greatly between individuals, and in humans it appears to be dependent on the presence of specific organisms and is produced in about half of normal individuals (McKay, Eastwood et al. 1985). Recently, it has been shown that physiological concentrations of methane slow small intestinal transit by augmenting ileal circular muscle contractions (Pimentel, Lin et al. 2006). In addition, when methane is the bacterial fermentation product in human patients with irritable bowel syndrome, those patients almost universally suffer from constipation, and small intestinal contractile activity and discomfort are increased in irritable bowel syndrome patients who produce methane (Pimentel, Lin et al. 2006; Pimentel, Mayer et al. 2003). Thus the induction of nonpropulsive segmental contractions by methane may be a cause of motility dysfunction in dogs and cats. Consequently, the supplementation of diets with rapidly fermentable purified fiber sources such as hydrolyzed guar gum may exacerbate some cases of constipation, IBS, and other diseases that involve disturbances of motility.

Thus, individualization is key to successful dietary modification in patients with chronic constipation. When colonic motility is known or suspected to be impaired (e.g., megacolon), low-reside diets with moderate (<10% DMB) contents of total dietary fiber are recommended. When colonic motility is still suspected to be reasonable, increasing nonfermentable, gel-forming fiber is likely to be beneficial. A total dietary fiber content of 10–20% DMB is reasonable.

Intestinal Gas and Flatulence

Intestinal Gas Transit and Borborygmus

Gas that is present in the small and large intestine can originate from aerophagia or be endogenously formed. Intestinal CO_2 is mostly formed from the reaction between bicarbonate and gastric acid producing water and CO_2 in the upper small intestine. For each mol of H^+ neutralized by pancreatic HCO_3^-, 1 mol of CO_2 is produced. In the 3 hours following a meal, a dog may produce 6 mEq H^+, which will result in the production of 134 mL CO_2 (Thor, Copeland et al. 1977). Most of the CO_2 diffuses into the circulation but some remains within the luminal contents. The remaining gases are produced from microbial fermentation, predominantly in the distal small intestine and colon.

Gas is moved along the intestine independently of solids and liquids, and in humans gas transit is more effective in the erect than supine position illustrating the active propulsion of gas (Dainese, Serra et al. 2003). The rate of gas passage is influenced by dietary fat, but not by the moisture content of the diet (Gonlachanvit, Coleski et al. 2006). Intestinal gas can be rapidly propelled aborally in normal dogs such that the infusion of air at 2 mL/min does not produce apparent abdominal discomfort (Pimentel, Lin et al. 2006). In humans, up to 30 mL/min can be infused jejunally without discomfort. Gas is actively propelled by a sustained contraction proximal to the gas, but it is still not known if intestinal gas induces classical peristaltic waves responsible for the movement of liquid and solid ingesta (Tremolaterra, Villoria et al. 2006). Following a meal, the presence of lipid within the duodenum induces intestinal relaxation and leads to an increase in the intraluminal pool (Hernando-Harder, Serra et al. 2004). In humans, drinking water does not influence gas transit, while food increases the rate of transit and volume of gas that reaches the anus (Gonlachanvit, Coleski et al. 2006). The presence of duodenal lipid has the most profound inhibitory affect on gas transit times, while fiber (psyllium husk) also slows intestinal gas transit, as well as increasing the volume of gas produced from fermentation (Hernando-Harder, Serra et al. 2004; Harder, Hernando-Harder et al. 2006; Gonlachanvit, Coleski et al. 2004). In contrast, the intestinal transit of gas is not influenced by the moisture content of the diet (Gonlachanvit, Coleski et al. 2006).

In humans, the retention of infused gas can be halved and the retardant effect of duodenal lipid can be reversed by gentle physical exercise (peddling on an adapted bicycle ergometer not sufficient to raise heart rate or blood pressure) (Villoria, Serra et al. 2006). Although not directly studied in dogs, flatulence is reported less frequently by owners of dogs that exercise frequently than by owners of sedentary dogs (Jones, Jones et al. 1998).

Borborygmus can result from excessive intestinal gas or altered motility. Humans with irritable bowel syndrome

who have bloating and borborygmus as symptoms have impaired gas transit and develop intestinal gas retention, intestinal distension, and pain in response to gas loads that are well tolerated by normal individuals (Passos, Serra et al. 2005). In those patients, proximal intestinal gas rather than large intestinal gas is responsible for their symptoms (Salvioli, Serra et al. 2005).

Flatulence

The dominance of atmospheric gases in flatus illustrates that ingested gas forms the largest component. However, odiferous compounds are the result of microbial fermentation of luminal contents. In dogs, flatulence is more likely to occur within 2 hours of feeding, although the presence of sulfur gases is not temporally related to feeding (Yamka, Harmon et al. 2006; Collins, Perez-Camargo et al. 2001). Thus ingested air is likely rapidly transported and passed after a meal, while fermentative by-products may accumulate at other times. Malodor is strongly correlated with the presence of hydrogen sulfide, and the production of hydrogen sulfide is highly variable among animals fed the same diet (Collins, Perez-Camargo et al. 2001). Sulfur gases are produced by sulfate-reducing bacteria such as the genera *Desulfotomaculum*, *Desulfobacter*, *Desulfomonas*, and *Desulfobulbus*, and differences in sulfur gas production between animals likely represents differences in microflora (Gibson, Macfarlane et al. 1988). Sources of sulfur compounds for fermentation include endogenously derived amino acids from mucin, sulfate in cruciferous vegetables and nuts, and poorly digestible sulfated polysaccharides such as the gelling agent carrageenan.

As noted above, fiber slows intestinal gas transport, but fermentable fiber is also a substrate for the luminal production of intestinal gas, and in normal humans, fiber intake is positively associated with the number of daily flatus emissions (Gonlachanvit, Coleski et al. 2004; Bolin and Stanton 1998; Marthinsen and Fleming 1982; Tomlin, Lowis et al. 1991). Thus, high-fiber diets can increase gas production by colonic flora and inhibit gas transit leading to gas retention, notable borborygmus, abdominal pain, and flatulence (Gonlachanvit, Coleski et al. 2004). Ingestion of a "fiber-free" diet for 48 hours significantly reduces the total volume of flatus (Tomlin, Lowis et al. 1991). Highly purified, highly fermentable fibers will increase flatus volumes more than nonfermentable fiber and will also alter the composition of the flatus. For instance, xylan and pectin cause higher flatus volume, hydrogen, carbon dioxide, and methane levels than cellulose or corn bran (Marthinsen and Fleming 1982). In addition, intestinal and/or microbial adaptation to changes in fiber content has been demonstrated such that flatus volumes do not stabilize until 2 to 5 days of feeding have accrued (Marthinsen and Fleming 1982).

The exact nature of flatus then is affected by the composition and quantity of diet fed, its digestibility, and the type and abundance of bacterial flora. Any disease causing maldigestion or malabsorption will increase and alter the substrate available for fermentation and will thus alter the volume and odor of flatus produced.

In the absence of a primary diagnosis, the symptomatic management of borborygmus and flatulence should begin with a change to a highly digestible, low-fat diet. As with any dietary variable, there is no absolute value that constitutes "high" or "low," and they remain relative terms. Importantly, an attempt should be made to introduce a diet that has a greater digestibility and a lower fat content than the current diet. Empirical choices would be select protein diets with less than 20% ME as fat. Hydrolyzed protein diets have a high protein digestibility, and most contain highly digestible carbohydrate sources as well; however, the fat content may be greater than ideal. Diets with fermentable fiber sources (e.g., gums, carrageenan, pectins, resistant starches) in greater concentrations than the current diet should be avoided (Tomlin, Lowis et al. 1991). Empirically, crude fiber contents of less than 3% would probably suffice.

Alternatively, the owner can prepare a homemade diet comprising highly digestible protein and carbohydrate sources appropriately balanced with vitamins and minerals. Suitable home-prepared diets for managing acute gastroenteritis or dietary indiscretion in dogs and cats include cottage cheese (1% milk fat) and boiled white rice (1 : 1 wgt : wgt), or chicken and rice (1 : 4 wgt:wgt). Cottage cheese and boiled white rice (1 : 1) provides 33% protein, 6% fat, and 61% carbohydrate as a percentage of kJs or kcals. It contains 4.8 kJ/g or 1 kcal/g as fed. Therefore, it is an ideal macronutrient profile, with an easy energy density to calculate the amount to feed. For diagnostic and short-term purposes, nutrient balancing of the diet is unnecessary, and these diets can be fed safely to a previously well-nourished animal for at least 7 days without concern.

The possibility of food hypersensitivity should also be considered in any patient with chronic flatulence or borborygmus, and novel or hydrolyzed protein diets should be introduced. It is recommended that a short-term switch to a highly digestible, low-fat diet be considered prior to concerns of novelty. If the initial dietary change is unsuccessful, a home-prepared or commercial novel or hydrolyzed protein should be tried. Of course, an ideal initial

management of both acute and chronic borborygmus and flatulence is to feed a diet that is both novel or hydrolyzed, and that is highly digestible, very low in fat, and very low in fermentable fiber. Appropriately balanced home-prepared recipes are probably the only diets that achieve all the stated goals.

As mentioned before, flatulence is reported less frequently by owners of dogs that exercise frequently than by owners of sedentary dogs (Jones, Jones et al. 1998). The effect of exercise would be consistent with findings in humans. It is not known, however, if the timing of exercise relative to meals is important, nor what amount of exercise is required. Experiments in humans suggest very little activity is necessary to promote gas movement. On that basis, it is prudent to recommend an increase in daily exercise for dogs, and to encourage physical activity in cats for whom flatulence is problematic.

Increasing the frequency of feeding is often suggested as a potential therapy for flatulence, ostensibly to slow the delivery of nutrients to the small intestine and allow a greater digestion or absorption. In normal pigs, increasing the feeding frequency from once to twice daily increased protein digestibility in one study, but not in another (Mroz, Jongbloed et al. 1994; Holt, Johnston et al. 2006). In pigs with ligated pancreatic ducts there was no effect of the frequency of feeding on digestibility (Kammlott, Karthoff et al. 2005). There is no evidence that changing the frequency of feeding has any effect on digestibility in dogs or cats. A study of flatulence in dogs revealed a decrease in the frequency of flatus in dogs fed twice (9.9 flatuses/day) compared with once (13.5 flatuses/day) per day. (Yamka, Harmon et al. 2006) Owners of dogs fed more than once per day did not report flatulence in their dogs more frequently than owners that fed only once daily (Jones, Jones et al. 1998). Thus, increasing the frequency of feeding may, in some dogs or cats, decrease flatulence, but at best the effect is mild.

Symptomatic therapy for eructation centers on attempts to reduce aerophagia. However, there are no studies that have evaluated the efficacy of methods for reducing aerophagia. Avoiding situations that provoke nervousness and by discouraging greedy eating (for instance, by ensuring a dog does not have to compete for his food) may be helpful. Feeding multiple small meals may reduce the gastric distension secondary to aerophagia by allowing sufficient time between a series of mouthfuls for eructation to occur. Head elevation may reduce aerophagia in some dogs but could also increase it with others.

In the rare event that dietary manipulation and regular exercise are not successful in eliminating signs, the patient should be evaluated for the presence of organic or functional intestinal disease such as described for small intestinal diarrhea. Alternatively, symptomatic pharmacologic management can be tried.

SUMMARY

- Timing and frequency of feeding, route of feeding, and macronutrient and micronutrient compositions of the diet have profound influences on oral and intestinal health. There is also a considerable indirect effect through dietary influences on the intestinal microflora.
- Periodontal disease is the most common disease affecting domestic dogs and cats. Although chewing activities and dietary additives may be sufficient to reduce plaque or even prevent calculus, only those activities that provide appropriate gingival stimulation will prevent gingivitis and periodontitis.
- Elevated feeding to promote passage via gravity is usually recommended in patients with megaesophagus, whatever food is selected. Hand-feeding chunks of meat or meat balls while the patient remains in a seated position is very effective.
- The main feeding concern for patients with esophagitis is the risk of promoting gastroesophageal reflux. The most important variables that increase gastroesophageal reflux induced by a meal are volume, total energy content, osmolarity, rate of ingestion of the meal, and possibly postprandial exercise.
- In cases where oral feeding is not possible in patients with esophageal disease, gastrostomy tube placement is indicated.
- The optimal nutritional approach for dogs and cats with inflammatory bowel disease remains to be determined and certainly varies from animal to animal. Regardless of the underlying etiology for any given patient, abnormal immune responses to dietary antigens are often suspected, and the clinical response to novel protein diets supports that hypothesis.
- When severe lymphangiectasia accompanies IBD, priority should be given to the feeding of a restricted-fat diet over antigenic novelty, since the hypoproteinemia is often the most life-threatening derangement.

- The ideal diagnostic and long-term diets for patients with adverse food reactions are based mostly on protein novelty, or protein hydrolysis.
- Dehydration, generalized protein-calorie malnutrition, and multiple nutrient deficiencies can result in animals with short bowel syndrome. Simple compensation through increased intake may be sufficient in mildly affected cases, but the majority require significant dietary adjustment.
- Overall recommendations for the management of chronic colitis are to first change to a novel or hydrolyzed protein diet. If an initial response to dietary manipulation is not successful, adjust the dietary fiber content.
- Idiopathic large bowel diarrhea may respond to increased dietary fiber or may be responsive to other dietary manipulations for reasons that are not clear. Failure to respond to one empirical dietary manipulation (e.g., the addition of fiber) should not sway the clinician away from further empirical dietary choices.
- When colonic motility is known or suspected to be impaired (e.g., megacolon), low-residue diets with moderate (<10% DMB) contents of total dietary fiber are recommended. When colonic motility is still suspected to be reasonable, increasing nonfermentable, gel-forming fiber is likely to be beneficial.
- In the absence of a primary diagnosis, the symptomatic management of borborygmus and flatulence should begin with a change to a highly digestible, low-fat diet. Feeding small multiple meals and increasing activity may also help manage these conditions.

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Nutritional Management of Exocrine Pancreatic Diseases

13

Cecilia Villaverde

The main function of the exocrine pancreas is to synthesize and secrete substances to allow for the proper digestion and absorption of food. The pancreas synthesizes and secretes digestive enzymes that break down protein, fat, and carbohydrates into their smaller, absorbable components. These enzymes are secreted as inactive zymogens, which are kept separate from lysosomes in the pancreatic tissue to avoid premature activation. Other protection mechanisms include pancreatic trypsin inhibitors present in pancreatic juice (which can inactivate free trypsin) and antiproteases present in plasma (such as alpha-macroglobulin) that capture proteases that escape into circulation (Mansfield and Jones 2001).

The pancreas also secretes bicarbonate, to reach optimal pH in the small intestine for enzyme activity; intrinsic factor, to allow absorption of vitamin B12; and bacteriostatic substances to prevent bacterial proliferation in the small intestine.

Diet plays an important role regulating pancreatic secretion (Strombeck 1996). A complex system involving the nervous and endocrine systems is responsible for pancreatic secretion regulation. The cephalic phase is mediated by the autonomous nervous system. The gastric phase is mediated by gastrin, a hormone released in response to gastric distention and the presence of nutrients (such as protein). The intestinal phase is mediated by cholecystokinin (CCK) and secretin (also gastrin and vasoactive intestinal peptide), which are hormones synthesized by the intestinal mucosa. Secretin release is stimulated by the presence of acid in the intestine and intraluminal fatty acids (Watanabe et al. 1986). CCK secretion is stimulated by amino acids, acidic pH, and long-chain fatty acids (see Fig. 13.1). CCK not only stimulates pancreatic secretion, it also results in delayed gastric emptying and voiding of the gall bladder.

The relative potency of different nutrients to stimulate CCK secretion seems to be species specific. In humans, amino acids, protein, and long-chain triglycerides are more effective than carbohydrates (Karhunen et al. 2008). In dogs, fatty acids (Sun et al. 1992), amino acids, and peptides stimulate CCK release, but intact proteins do not (Meyer and Kelly 1976). Cats secrete CCK in response to long-chain triglycerides and proteins (Backus, Rosenquist et al. 1995). Although amino acids also stimulate CCK release, intact protein is more potent in felines (Backus, Howard et al. 1997).

PANCREATITIS

Pancreatitis is defined as inflammation of the pancreas. Currently there is no standardized classification of the disease in veterinary medicine. One way of classification is to extrapolate from human medicine as acute or chronic (Steiner and Williams 1999; Williams and Steiner 2005). Acute pancreatitis refers to inflammation that completely resolves with removal of the inciting cause, whereas chronic pancreatitis is characterized by irreversible histopathological changes in the pancreas (such as fibrosis and atrophy).

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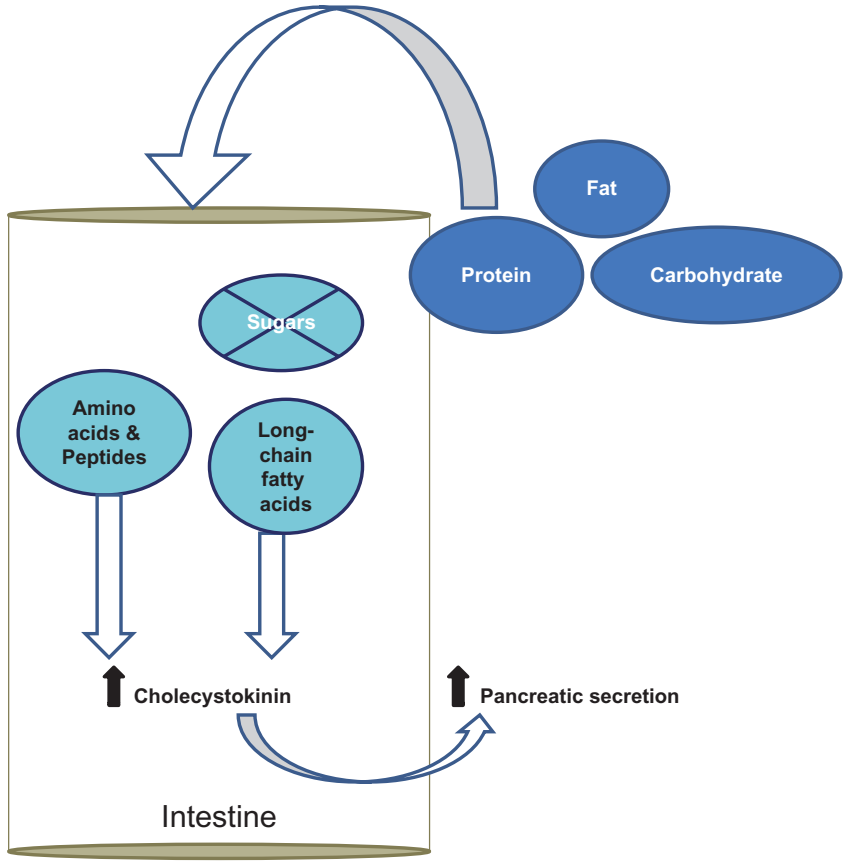

Fig. 13.1. Response of cholecystokinin secretion by intestinal mucosal cells to different macronutrients in the small intestinal lumen.

The differentiation is based on histopathology and not on clinical signs, although canine acute pancreatitis tends to be of sudden onset, with severe clinical signs, and is often associated with systemic complications, while chronic pancreatitis has milder clinical signs and a more insidious course. This is less true in the feline, where a study has shown that there is a poor correlation between clinical signs and histopathology findings (Ferreri et al. 2003). Histopathologically, chronic pancreatitis is the most common form of the disease in cats (De Cock et al. 2007).

The main clinical signs in dogs include vomiting and abdominal pain, and also depression, anorexia, fever, and diarrhea (Williams and Steiner 2005). In cats, signs are highly variable and can be quite vague; most commonly lethargy and anorexia are reported (Hill and Van Winkle 1993; Ferreri et al. 2003). Chronic cases can be subclinical or result in hyporexia and weight loss. Clinical signs can be associated with comorbidities. In cats, pancreatitis can be associated with hepatic and/or gastrointestinal disease (Weiss et al. 1996), and it is also a comorbidity found in dogs and cats with diabetes mellitus (Hess, Saunders, Van Winkle et al. 2000; Forcada et al. 2008).

Diagnosis of pancreatitis can be difficult, especially in cats. Clinical examination findings and standard blood analysis (complete blood cell count, serum biochemistry) show nonspecific alterations (Steiner 2003). Lipase and amylase increases, which have been traditionally used to diagnose pancreatitis, are neither sensitive nor specific enough to be reliable tests (particularly in cats) (Steiner 2003; Xenoulis and Steiner 2008). Ultrasound can be an effective diagnostic tool (Hess, Kass et al. 1999). One study in cats found that abdominal ultrasound had a sensitivity of 80% and specificity of 88% (Forman et al. 2004), but it has been suggested that these values might change depending on the operator (Xenoulis and Steiner 2008). Specific tests measuring pancreatic lipase have

been developed for dogs (cPLI) and cats (fPLI). The cPLI test is specific and sensitive for the disease (Steiner 2003). One study found that fPLI had a sensitivity and specificity of close to 100% in cats with moderate to severe disease (Forman et al. 2004). The less severe the disease, the less sensitive is this test (Xenoulis and Steiner 2008). Definitive diagnosis is made by histopathology. Even so, the diagnosis can be missed in a biopsy due to the distribution of the inflammation (Steiner 2003).

Pathophysiology

It is widely thought that pancreatitis develops as a consequence of pancreas autodigestion resulting from premature activation of the zymogens within the acinar cells (Steiner and Williams 2005; Williams and Steiner 2005). How the protective mechanisms of the pancreas are overwhelmed and autodigestion is initiated, though, is unclear and an underlying cause is rarely identified.

Experimental pancreatitis can be initiated by hyperstimulation with CCK analogs (Morita et al. 1998; Saluja et al. 2007), but the importance of these mechanisms in spontaneous disease is unknown.

Risk factors in dogs include hereditary, hyperlipidemia, drugs [such as phenobarbital and potassium bromide (Gaskill and Cribb 2000; Steiner, Xenoulis et al. 2008)], trauma, and ischemia. Nutrition-related risk factors include obesity and high-fat/low-protein diets (Hess, Kass et al. 1999; Williams and Steiner 2005; Lem et al. 2008).

In one retrospective study, 26% of dogs with fatal acute pancreatitis were hyperlipidemic (Hess, Saunders, Van Winkle et al. 1998), but it is not present in all natural cases of pancreatitis (Whitney et al. 1987). Hyperlipidemia can be the cause or result of pancreatitis. The proposed etiologic mechanisms include the formation of toxic fatty acid products within the pancreas due to high triglycerides in pancreatic capillaries, formation of microthrombi by fatty acids, and formation of damaging calcium soaps (Petersen et al. 2009; Tsuang et al. 2009). Some breeds are considered at higher risk for pancreatitis due to their predisposition to hyperlipidemia (such as Miniature Schnauzers, Shetland Sheepdogs, and Siamese cats).

A recent retrospective paper (Lem et al. 2008) noted that ingestion of unusual food items, intake of table scraps, and garbage eating were associated with a higher risk of pancreatitis. They also found a positive association of obesity with pancreatitis. One study (Akol et al. 1993) found that 43% of dogs with acute pancreatitis were overweight or obese. Another study also reported an association between being overweight and acute fatal pancreatitis in dogs (Hess, Kass et al. 1999).

In cats, there is much less information, and most cases are called "idiopathic" (Mansfield and Jones 2001; Steiner and Williams 2005). Less commonly, pancreatitis in cats has been associated with trauma and feline infectious peritonitis (FIP). Potential causes include hyperlipidemia, toxins, ischemia, and ascending infections. Increased age and gastrointestinal and liver diseases have been positively associated with chronic pancreatitis (Akol et al. 1993; Weiss et al. 1996; De Cock et al. 2007). The link between fatty foods, table scraps, and obesity with pancreatitis in cats has not been proven.

Nutritional Management

Controversies Regarding Nutritional Management

The management of the pancreatitic patient (especially cats) is quite controversial and more research in this area is needed. Some of the more conflicting points are presented in this section.

When to Start Feeding in Acute Pancreatitis?

Traditional approaches to the patient with pancreatitis, especially if vomiting, consist of "resting the pancreas" by withholding food and water for 24 to 48 hours or as long as vomiting persists. The goal is to minimize pancreatic stimulation by nutrients and minimize enzyme secretion. A secondary goal is to prevent aspiration pneumonia. Moreover, some of these patients have severe abdominal pain, which may be further compounded by feeding.

This approach has been recently challenged. There is one study in dogs with parvovirosis (Mohr et al. 2003) in which the dogs that underwent early enteral nutrition despite vomiting (within 12 hours of admission) recovered earlier and gained more weight than the dogs that were not fed until vomiting stopped for at least 12 hours (an average of 50 hours after admission). The authors hypothesize that early nutrition might have prevented malnutrition and improved the barrier function of the gut, thus improving outcome. It is unclear if a similar positive effect of early enteral nutrition would be seen in patients with pancreatitis, which has a very different pathophysiology from a viral enteritis.

In a study with dogs and experimentally induced disease (Qin, Su, Hu et al. 2003), early intrajejunal feeding did increase the plasma levels of CCK and other enteral hormones compared to parenteral nutrition; however, this did not result in an increase in pancreatic enzyme secretion. This suggests that the inflamed pancreas may not respond to nutrients the same way as the healthy pancreas. In addition, the animals fed enterally were not clinically worse, and results suggested that their guts were healthier and that

bacterial translocation was lower compared to the dogs fed parenterally (Qin, Su, Hu et al. 2002). However, information on enteral nutrition in naturally occurring disease is still lacking.

In humans, one recent meta-analysis of clinical trials reported the benefits of nutritional support (either parenteral or enteral) versus fasting on mortality (Petrov, Pylypchuk et al. 2008). This study showed that enteral nutrition was superior to parenteral regarding infectious complications. Another meta-analysis of clinical trials by the same authors compares enteral and parenteral nutrition and shows that enteral nutrition results in less infectious complications, and less risk of multiple organ failure, but only if nutrition is initiated within 48 hours of admission, which supports initiating nutrition as early as possible.

There are basically no studies in cats on the effect of nutrition on pancreatitis. However, due to the risk of hepatic lipidosis in fasting cats (Armstrong and Blanchard 2009), nutrition should be instituted as soon as possible, especially since vomiting is not a common clinical feature of pancreatitis in cats (Ferreri et al. 2003). Some authors recommend starting nutrition when the cat has been anorexic for 3 to 5 days (Zoran 2006; Chan 2009). In some cases, this might require the placement of a feeding tube. In cats, the most common is an esophageal feeding tube, as seen in Fig. 13.2.

How Low is a "Low-Fat" Diet?

The generalized use of terms like "low-fat" or "high-fat" is confusing because there is no established definition of what is a "normal" dietary fat level. This problem is further compounded by the different ways in which it is possible to express the amount of fat a foodstuff has. The most common are percentage as is or as fed (this is the way pet food labels report fat), percentage of dry matter, and percentage of metabolizable energy (ME). Ideally, percentage of the ME is the ideal way to compare different foods, since it allows for comparison between different foods with varying amounts of moisture, fiber, and ash. The fat content of commercial canine and feline diets ranges from 20% to levels as high as 70% on an ME basis. As a rule (but not always), feline diets are higher in fat than canine diets, and canned diets are higher in fat than dry diets. For most of the population eating commercial diets, a diet that has less than 20% fat on an ME basis will be considered low fat, but the term "low fat" is relative to the patient's original diet. This is especially important in animals with hyperlipidemia, where fat restriction has to be made relative to the current diet that is causing problems.

Fig. 13.2. Cat with pancreatitis and concurrent hepatic lipidosis with an esophageal feeding tube in place.

It is important to note that the diets marketed for the management of gastrointestinal disorders vary greatly in fat content, and the diet chosen may or may not be low fat depending on the diet history of the patient.

How Important is Fat Restriction in Feline Pancreatitis?

There is a paucity of data regarding pancreatitis in cats in general, and more so regarding the effect of diet on pancreatitis management in this species. As mentioned before, intact protein and triglycerides both stimulate CCK, whereas carbohydrates have only a weak effect (Backus, Rosenquist et al. 1995), so fat restriction may be indicated. Dietary fat also decreases gastric emptying and slows down gastrointestinal transit time (Strombeck 1996), which may be undesired in patients with gastrointestinal disease.

However, as opposed to dogs, high-fat foodstuffs have never been associated with naturally occurring pancreatitis in cats. There is currently no data to recommend for or against moderate or severe fat restriction in these patients. Fat restriction in cats can be challenging, since low-fat commercial diets for cats are also high in fiber and, thus, are not the first choice for patients with gastrointestinal problems. In this author's experience, it is reasonable to try a low-fat diet in cats with hyperlipidemia and when other approaches are not giving the desired results.

Dietary Management

The main goals to manage the patient with pancreatitis are to provide enough calories and nutrients to support recovery while decreasing pancreatic stimulation. This can be accomplished in a variety of ways and will vary depending on the clinicians' personal experience. The flowchart pre-

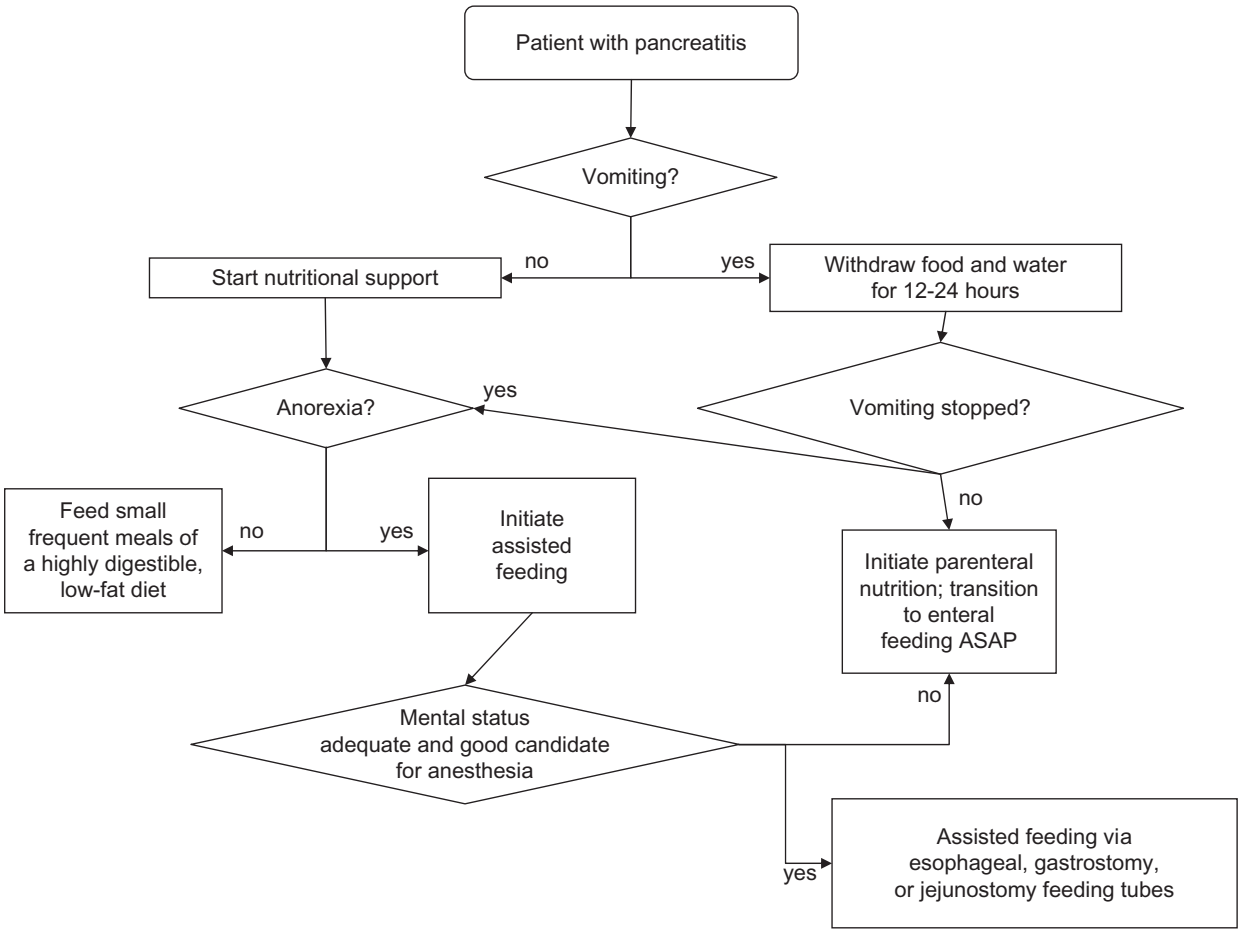

Fig. 13.3. When and how to start nutritional support.

sented in Fig. 13.3 can be used as a guide to decide if, when, and how to initiate nutritional support for each individual patient.

When to Feed

As a general rule, nutritional support should be instituted as soon as feasible. As discussed before, traditional recommendations include "resting the pancreas" by restricting oral intake of food and water until clinical signs abate. Before offering any food, water should be offered first. If water is well tolerated, feeding the animal a low-fat, highly digestible diet is indicated.

Cats that have been anorectic for more than 3 days should be fed as soon as possible despite the presence or absence of clinical signs in order to avoid hepatic lipidosis.

Route of Feeding

Enteral feeding is preferred if at all possible to avoid enterocyte atrophy and bacterial translocation and to keep costs down. If the patient is anorectic, nutritional support is indicated. Esophagostomy and gastrostomy tubes are indicated if the risk for aspiration pneumonia is minimal. If there is risk of aspiration, jejunostomy feeding tubes can be used to feed enterally while minimizing pancreatic stimulation (Ragins et al. 1973). The main challenge with jejunostomy tubes is the need for anesthesia and surgery for placement. There is one report (Jennings et al. 2001) where a feeding tube was placed in the jejunum of a cat with pancreatitis via a percutaneous endoscopic gastrostomy (PEG) tube. This technique, while still uncommon, may prove a viable alternative in the future to surgically placed jejunostomy tubes.

Nasoesophageal or nasogastric feeding tubes are also an option, especially if the patient is not a good candidate for anesthesia. Due to their small lumen size they can only be used with liquid diets, thus limiting diet choices and making it more difficult to provide a patient's full caloric requirements. There are no fat restricted liquid veterinary enteral formulas at this point. Some human enteral formulations are adequately low in fat but are only adequate for short-term management due to cost and nutritional inadequacy for dogs and cats.

Parenteral nutrition is indicated in cases of intractable vomiting, the patient is obtunded or cannot protect its airway for any other reason, and when feeding tubes cannot be placed due to instability for anesthesia. Gut atrophy has been proposed as a possible complication of parenteral nutrition in animal models (Frost and Bihari 1997; MacFie et al. 2006); thus, trickle feeding with a nasogastric/nasoesophageal tube if at all possible (for example 10% of the total daily calories) with a low-fat human enteral diet could potentially help maintain gut integrity.

Lipid emulsions can be included in parenteral nutrition solutions, since intravenously administered fat has not been associated with worsening the disease or stimulating the pancreas (Meier et al. 2006). If the patient is hyperlipidemic, fat in the solution should be minimized to keep serum triglycerides as low as possible (Chan and Freeman 2006).

Diet Selection

An ideal diet for the dog with acute pancreatitis is highly digestible, low in fat, and palatable. A good starting point is a mixture of cottage cheese (2% milk fat) and white rice (in a ratio of 1 : 1 v/v), which provides ~220 kcal per 8-fl oz cup (236.6 mL) and 10% fat on an ME basis. After 2 to 3 days, if well tolerated, the animal can be transitioned to a commercial diet.

This mixture can also be blenderized and fed through an esophagostomy or gastrostomy feeding tube if the patient is anorectic.

In cats, diets marketed for the management of intestinal disease can be used orally or via a feeding tube. If a low-fat diet is desired, the mixture of cottage cheese and rice can be used. If it is not palatable, other options include tuna (in water) plus baby rice cereal, or chicken breast plus baby rice cereal. For example, 3/8 cup of cooked roasted chicken breast (skinless and boneless) plus 3/4 cup of baby rice cereal (measured dry before reconstitution) provide ~200 kcal and 14% fat on an ME basis. Mixing 2 weight ounces of tuna in water (drained solids only) with 7/8 cup of baby rice cereal (measured dry before reconstitution) also provide ~200 kcal and only 9% fat on an ME basis.

If a jejunostomy tube is placed, low-fat diets are still preferred, since there is still some pancreatic stimulation, as suggested by one study with experimentally induced disease in dogs (Qin, Su et al. 2003). Due to the size of the tube and the lack of elasticity of the jejunum, liquid diets have to be used, ideally delivering via constant rate infusion to avoid overloading the gut.

It has been proposed that the diet fed through a jejunostomy tube should also be "elemental" to mimic what would normally be absorbed by the jejunum (proteins should be supplied in the form of free amino acids and short peptides while carbohydrates should be supplied as simple starches and sugars), but this is controversial even in human medicine (Niv et al. 2009). There is a meta-analysis in human pancreatitis patients that did not find any difference in outcome comparing "intact" versus "elemental" diets (Petrov, Loveday et al. 2009). There are no studies in veterinary medicine assessing the need for elemental formulations, so there are no data to support or reject the use of "intact" liquid diets.

Energy Requirements

During hospitalization, the goal is to provide the resting energy requirement (RER) initially (Chan and Freeman 2006). Once RER is provided, body weight and body condition should be monitored to adjust the amount of calories provided as necessary. A very slow increase in the calories provided is preferred to prevent metabolic derangements (critically ill animals in a catabolic state can often have significant electrolyte abnormalities) and to avoid overwhelming the gut. These patients are generally inactive during the hospital stay, and a conservative approach is necessary to avoid overfeeding issues. Sadly, our knowledge of energy requirements in critically ill animals is very limited.

Long-Term Management

In acute, one-time nonhyperlipidemic pancreatitis cases, it is frequently possible to go back to the dog's original maintenance diet, especially if the trigger has been identified (such as dietary indiscretion, "garbage gut," or drugs). A slow transition back to the original complete and balanced diet over several days is indicated.

However, in cases of chronic pancreatitis, hyperlipidemic animals, or recurrent acute pancreatitis a diet considerably lower in fat than the usual diet is indicated. In hyperlipidemic animals, a diet low enough in fat has to be selected to maintain fasting triglycerides within acceptable

ranges (see Chapter 17) and to prevent further pancreatitis episodes. In animals with chronic pancreatitis the approach is the same.

The diet selection will depend on the previous diets used. If the original diet is higher in fat (i.e., >35–40% fat on an ME basis), many commercial options are acceptable. However, if that is not the case, sometimes home cooking is the best option for the patient. The lowest fat commercially available canine diet is currently Royal Canin Veterinary Diet Gastrointestinal Low Fat Canine (~15% fat on an ME basis for both canned and dry).

Currently for cats, the lowest fat canned veterinary diet is Hill's Prescription Diet feline r/d (24% on an ME basis) and the lowest fat dry veterinary diet is Purina Veterinary Diet OM feline (21% on an ME basis). However, these diets are very high in fiber (thus, less digestible) and are not energy dense. Thus, they are not typically one's first choice in severe feline pancreatitis. In general, finding low-fat diets in cats is very challenging, since they tend to be lower in carbohydrates than canine diets and protein is an expensive ingredient. In general, therapeutic diets formulated for intestinal disease are used for these patients; however, they can vary greatly in their fat content and their effect on the patient should be carefully monitored via control of any hypertriglyceridemia, clinical signs, ultrasound, and pancreatic lipase measurements.

It is important to always check the fat level of diets and compare them to the previous diet. Some commercial foods marketed as lower or reduced fat are still too high in fat for pancreatitic patients. In some cases the difference in percentage of fat between the canned and the dry products is drastic.

In obese dogs, due to the epidemiological link between obesity and pancreatitis (Lem et al. 2008), a weight loss plan using a weight loss diet lower in fat than the previous diet is indicated until an ideal body condition score is reached (please see Chapter 9 on weight management).

Pancreatitis is a very challenging disease, both to diagnose and to treat, and there is no agreement upon the best way to manage it nutritionally. In the author's experience, using very low fat diets (especially in acute cases) enterally as soon as the vomiting is controlled is appropriate and prudent. Provision of adequate energy is not sacrificed with this approach. If enteral nutrition is not possible, the parenteral route may be considered. Long-term management will depend greatly on the previous diet history, concurrent diseases, and response to treatment. There are hundreds of diets available that might work for individual patients, and in some cases, a complete and balanced home-cooked diet may be the best option to control clinical signs.

Foods to Avoid in Chronic Pancreatitis

A good diet history is crucial in order to determine the level of dietary fat that is tolerated by the individual patient, especially in canine acute pancreatitis. If the pancreatitis episode was associated with the ingestion of a particular food item, efforts should be made to determine the level of fat of that particular food and avoid feeding close to or above that fat level in the future.

In any case, a patient diagnosed with chronic pancreatitis should be fed foods (complete and balanced diets, treats, and human foods) low or moderate in fat, to avoid recurrence of disease. Protein is the second most important nutrient in stimulating CCK, so very high protein diets should also be avoided especially in the feline patient.

Some commercial therapeutic diets are very high in fat. These include energy dense diets that use fat as a concentrated energy source (such as recovery- or convalescence-type diets), low-carbohydrate diets that use fat as the main energy source (such as feline diabetes management diets), and protein-restricted diets that are high fat to promote palatability (such as diets formulated for renal disease, liver disease, and even urolithiasis). In patients with pancreatitis and concurrent diseases such as kidney insufficiency, a home-cooked diet to accommodate the nutritional needs of each disease might be indicated.

There are a variety of over-the-counter diets that can also be very high in fat and sometimes in protein. Some examples include the carnivorous-type diets that do not use grains in their formulation, some raw-meat diets, and some very palatable sausage-like diets. It is important to point out that the fat content of all these diets can vary greatly between the dry and the canned formulation.

Some commercial treats can be very high in fat and protein, especially the meaty ones and should be avoided. Carbohydrate-based biscuits are generally acceptable.

Regarding food usually used for human consumption and table scraps, fruits and vegetables are excellent treats for pets with chronic pancreatitis, since they are mostly carbohydrate and are also low in energy density, which helps prevent undesired weight gain. Some common human foods to avoid are listed in Table 13.1.

EXOCRINE PANCREATIC INSUFFICIENCY

Pathophysiology

Exocrine pancreatic insufficiency (EPI) results from a severe loss of exocrine pancreatic function. It has been reported that 90% of acinar cells must be lost before clinical signs arise (Westermarck, Wiberg et al. 2005).

There are several mechanisms by which pancreatic mass can be lost. In young dogs, the most common cause of EPI

Table 13.1. Common Foods to Avoid in Chronic Canine/Feline Pancreatitis

Fatty animal products	**Dairy**
Beef	Cheese (non low fat)
Lamb	Full-fat yogurt
Rabbit	**Commercial treats**
Goat	Meaty treats (sausage-like)
Cured meats	Dry meat treats (jerky)
Sausage	**Other**
Fatty fish	Tofu
Salmon	Peanut butter
Sardines	

(Westermarck, Wiberg et al. 2005) is pancreatic acinar atrophy (PAA), which has been described in German Shepherd dogs and other breeds such as Rough Coated Collies. The mechanisms of PAA are not completely understood. It is believed to have an important genetic component, and the published research supports that PAA is preceded by a lymphocytic infiltration of the pancreas (Wiberg et al. 1999), which has led to the hypothesis that PAA is an autoimmune disease. There is a case series, which suggests that chronic pancreatitis can also be a cause of EPI in dogs (Watson 2003), but its relative importance is unknown. Other less common possible causes of EPI in dogs include pancreatic hypoplasia and pancreatic neoplasia.

In cats it is believed that the most common cause of EPI is chronic pancreatitis that ends up destroying the acini (Steiner and Williams 1999). This process has also been demonstrated in humans (Gupta et al. 2009). Pancreatic acinar atrophy has not been described in the cat.

When the pancreas is unable to provide enough digestive enzymes, bicarbonate, and other substances for proper digestion and absorption, signs of fat, protein, and carbohydrate malassimilation occur, mainly weight loss, poor body condition, diarrhea (with steatorrhea), and polyphagia (Westermarck and Wiberg 2003; Thompson et al. 2009). Figure 13.4 shows a dog with a dull coat and very poor body condition, secondary to the maldigestion and malabsorption classical of this disease.

Due to fat malabsorption, fat-soluble vitamins (which need fat for proper absorption) might be deficient. One study found that serum vitamin A was lower in dogs with experimental EPI compared to control dogs (Adamama-Moraitou, Rallis, Prassinos et al. 2002). There is no information on macro and trace minerals absorption in patients with EPI. In one study in dogs with experimental EPI, the

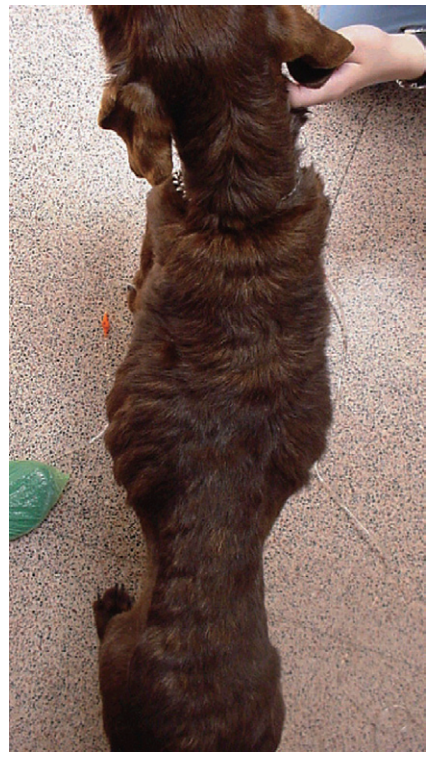

Fig. 13.4. Dog with exocrine pancreatic insufficiency.

investigators found lower serum and tissue concentrations of copper and zinc compared to control dogs, but it is unknown the significance of these findings (Adamama-Moraitou, Rallis, Papasteriadis et al. 2001).

The pancreas secretes intrinsic factor, essential for vitamin B12 (cobalamin) absorption. In dogs, the stomach also secretes it, but it is less important than the pancreas (Vaillant et al. 1990), and in the cat it seems the pancreas is the only significant source. Hypocobalaminemia has been reported in dogs (Simpson, Morton et al. 1989) and in cats (Thompson et al. 2009) with EPI. In dogs, this can be partly due to small animal intestinal overgrowth, which has been described in dogs (but not in cats) with EPI (Williams, Batt et al. 1987; Westermarck, Myllys et al. 1993).

Nutritional Management

Controversies Regarding Nutritional Management

Is A Low Fat Diet Important For Management?

Enzyme supplementation is the mainstay for the therapy of patients with EPI. The activity of lipase, however, never reaches levels comparable to healthy animals due to destruction by acid (DiMagno et al. 1977) and proteases

(Thiruvengadam and Dimagno 1988) in the stomach, and many treated patients still have some degree of steatorrhea. For this reason, feeding a low- to moderate-fat diet has been proposed as a strategy to limit fat malabsorption. A possible downside of severe fat restriction is reduction of energy density of the diet, which is not ideal in very underweight animals.

One study (Simpson, Maskell et al. 1994) found that a group of dogs with EPI gained weight after being treated with pancreatic enzymes and a low-fat diet. However, there was no control group, and the dogs continued to do well after they were switched to a variety of different diets.

Two papers from Westermack and collaborators (Westermarck Jinttila et al. 1995; Westermarck and Wiberg 2006) investigated the importance of fat restriction and diet change in managing dogs with EPI. In the first study, the effect of a low-fat diet (13% on an ME basis) was compared to the dogs' original diet (which varied in fat content from 14% to 30% on an ME basis, approximately). In the latter study, three diets were used: a high-fat diet (51% on an ME basis), a high-fiber, low-fat diet (22% fat on an ME basis) and a moderate-fat, highly digestible diet (30% fat on an ME basis). The most important finding of these studies was that response to fat restriction varied greatly from dog to dog: Some animals responded favorably, others were not affected, others were negatively affected. There are studies in experimentally induced EPI in dogs that suggest that fat restriction actually worsens lipase activity (Suzuki, Mizumoto, Sarr et al. 1997; Suzuki, Mizumoto, Rerkinimitr et al. 1999), since fat and protein protect lipase during aboral intestinal transit. Biourge and collaborators (Biourge and Fontaine 2004) published a case series where three German Shepherd dogs with EPI and concurrent skin disease attributed to an adverse reaction to food were treated with a hydrolyzed diet (soy based) and pancreatic enzyme supplementation. The three dogs did well with the diet and the supplementation, even though the fat content of this diet was high (40.8% on an ME basis). A retrospective study looking at dogs with EPI did not find a positive (or negative) effect of changing to a low-fat diet (Batchelor et al. 2007).

Thus, current information indicates that a low-fat diet is not necessary unless steatorrhea is uncontrollable, at least initially. There is no information published regarding the effect of dietary fat on feline EPI.

Are Medium-Chain Triglycerides Preferred Over Long-Chain Triglycerides?

Medium-chain triglycerides (MCTs) have medium-chain fatty acids (6 to 12 carbons) esterified to the glycerol moiety. They have been used in human medicine to manage malabsorption diseases, since it is believed that they are absorbed via the portal circulation instead of being transported in chylomicrons via lymphatic vessels. Research in cats and dogs is lacking.

Rutz and colleagues (2004) studied the effect of three diets (containing 0%, 16%, or 35% of the total fat content as MCTs) in a randomized controlled double-blind crossover trial. They found increased blood concentration of cholesterol and some fat-soluble vitamins, but there was no difference between the groups regarding appetite, attitude, drinking behavior, volume of feces, defecation frequency, color of feces, consistency of feces, flatulence, or borborygmus, as subjectively assessed by their owners.

High levels of MCTs have been associated with palatability problems in dogs (Matulka et al. 2009) and even low to moderate levels of MCTs seem to be unpalatable to cats (MacDonald et al. 1985). Currently, there is not enough positive evidence to support the use of MCTs in dogs and cats with EPI.

Dietary Management

The main treatment of EPI is lifelong enzyme replacement therapy (Westermarck, Wiberg et al. 2005). There are several commercial sources of these enzymes, although raw pancreas can also be used (using raw pancreas still carries the same risks associated with feeding any raw meat, including the potential to spread zoonotic diseases). These enzymes are given with every meal (with no need to preincubate them with food).

The main nutritional goals in patients with EPI are to provide enough energy and nutrients for an ideal body condition, avoid nutrient deficiencies, and minimize diarrhea. In light of the published data, it appears that there is not one single diet that can achieve these goals. In the most recent study from Westermack and Wiberg (2006), some dogs responded to diet change but to different types of diet depending on the patient. An individual choice of diet should be made for each patient, and in many cases this process will be one characterized by trial and error. Initially, a diet change might not be necessary (unless there is a concurrent disease that requires it, such as with adverse food reactions). Once enzyme supplementation has been in place for 3 to 4 weeks, the diet can be changed if the clinical response is not ideal. For example, since some enzymes can be affected by fiber, some authors recommend low-fiber (i.e., highly digestible) diets (Steiner and Williams 1999). Examples of highly digestible foods are the "intestinal" veterinary therapeutic diets. In dogs with

a poor body condition, a high-fat diet to promote fast weight gain might be attempted.

Regarding individual deficiencies, animals with low cobalamin should be supplemented parenterally with this vitamin until normalization. In both dogs and cats, hypocobalaminemia has been identified as a poor prognostic indicator (Batchelor et al. 2007; Thompson et al. 2009) and can be a reason for treatment failure.

SUMMARY

- Voluntary or assisted feeding should be instituted as soon as feasible in animals with acute pancreatitis. The main nutritional goal is to provide energy and nutrients while minimizing pancreatic secretion.
- Fat is the most potent stimulator for pancreatic secretion, and its oral intake must be restricted during an episode of acute pancreatitis. In chronic pancreatitis, lifelong fat restriction might be needed. Very high levels of dietary protein should also be avoided.
- Long-term nutritional management of acute pancreatitis should address any predisposing factors for the disease such as obesity, hyperlipidemia, and consumption of fatty foods.
- The existence of concurrent disease (such as intestinal or liver disease) should be considered accordingly when deciding on the nutritional management of the cat with pancreatitis.
- Nutritional goals for the management of exocrine pancreatic insufficiency are to provide energy for a healthy body condition, provide nutrients to avoid deficiencies, and minimize steatorrhea. A highly digestible diet can be useful in cases where regular maintenance diets fail to achieve these goals.
- Cobalamin deficiency is a cause for exocrine pancreatic insufficiency treatment failure and a poor prognostic indicator in dogs and cats and should be supplemented parenterally if present.
- Moderate- to high-fat diets can be useful in patients with exocrine pancreatic insufficiency with very poor body condition.
- The presence of concurrent diseases in dogs and especially cats will affect the diet choice in these patients with exocrine pancreatic insufficiency.

As for fat-soluble vitamins, they can be supplemented orally if there are signs of clinical deficiency (e.g., skin disease or coagulopathy). In many cases, feeding a complete and balanced diet and controlling the disease via enzyme supplementation seems to be sufficient.

In the only descriptive study of feline EPI (Thompson et al. 2009), 63% of the 16 cases had concurrent diseases, which might affect the dietary choice of these patients.

Regarding feed management, *ad libitum* feeding is not an option in these patients, since pancreatic enzymes are given with every meal. Also, it is important to avoid nonscheduled treats and to make sure that the patient does not have access to unmonitored food sources.

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Nutritional Management of Hepatobiliary Diseases

14

Stanley L. Marks

The unique position of the liver between the intestinally derived portal venous circulation and the systemic venous circulation make it susceptible to a myriad of inflammatory and degenerative conditions. Malnutrition is a common finding in patients with advanced hepatic disease and is an independent risk factor for predicting clinical outcome in human patients with chronic hepatic disease (Qiao et al. 1988). The liver is unique because it derives most of its own nutrient supply from a vein rather than an artery. Hepatotropic factors in portal venous blood modulate the functional and structural integrity of the liver (Diehl 1991). Several hormones, including insulin, glucagon, glucocorticoids, thyroid hormone, parathormone, calcitonin, α- and β-adrenergic agents, and insulin-like growth factors (IGF) I and II increase after hepatic injury or resection and may affect the ensuing hepatic regenerative growth (Bucher and Malt 1971). Optimal nutrition is important to help regulate the hormonal milieu after hepatic injury; however, the specific nutritional requirements of dogs and cats with liver disease have not been well defined to date.

Unlike most terminally differentiated cells, hepatocytes in adult liver retain the capacity to proliferate. After partial (70%) hepatectomy, compensatory hyperplasia begins within minutes of resection and is typically completed within 2 weeks in rats and in less than 1 month in people (Higgins and Anderson 1931; Francavilla et al. 1990). The management of dogs and cats with liver disease should thus be predicated on using this capacity to the maximum advantage.

METABOLIC ALTERATIONS IN LIVER FAILURE

Hepatocellular dysfunction is responsible for a number of metabolic disturbances that alter utilization of various nutrients by the body. Changes in protein, carbohydrate, and fat metabolism (Table 14.1) are particularly prominent in the fasting state (McCullough and Tavill 1991). Attempts to correct these alterations by manipulating nutrient supply represent an important strategy in the management of patients with significant hepatic disease. Impaired hepatic metabolism and storage may result in vitamin and mineral deficiencies. A combination of these problems usually exists in patients with hepatic disease and each must be given consideration before appropriate dietary therapy can be instituted.

Carbohydrate Metabolic Alterations

Advanced hepatic disease is often associated with a decrease in glycogen storage and glucose synthesis, contributing to fasting hypoglycemia. Hepatic glycogen can usually meet glucose needs (primarily for the brain) for 24 to 36 hours. In people with hepatic cirrhosis, glycogen stores are more rapidly depleted (10 to 12 hours), which results in premature protein catabolism to supply amino acids for gluconeogenesis (Owen et al. 1981). Fasting hypoglycemia is uncommon in patients with liver disease

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Table 14.1. Metabolic Alterations in Hepatic Failure

Alteration	Mechanism
Hyperglucagonemia	Portosystemic shunting
	Impaired hepatic degradation
	Increased plasma aromatic amino acids
	Hyperammonemia
Hyperinsulinemia	Increased peripheral insulin resistance
	Decreased insulin to glucagon ratio
	Impaired hepatic degradation
Increased plasma epinephrine and cortisol	Impaired hepatic degradation
Decreased liver and muscle carbohydrate stores	Accelerated glycogenolysis
	Impaired glycogenesis
Increased gluconeogenesis	Hyperglucagonemia
Hyperglycemia (fasting & postprandial)	Portosystemic shunting
	Increased gluconeogenesis
	Decreased insulin-dependent glucose uptake
	Decreased insulin-hepatic glycolysis
Increased plasma aromatic amino acids[a]	Decreased hepatic clearance and incorporation into proteins
	Increased release into the circulation
Decreased plasma branched-chain amino acids[a]	Hyperinsulinemia and excessive uptake
	Increased utilization as an energy source
Increased plasma methionine, glutamine, asparagine, and histidine[a]	Decreased hepatic clearance

[a]Tietge et al. 2003.

because euglycemia can be maintained with as little as one-fourth to one-third of normal liver parenchymal mass (Zakim 1982). In addition, fasting hypoglycemia is prevented by a compensatory drop in peripheral glucose oxidation. However, hepatogenic hypoglycemia can occur and is most common in dogs with cirrhosis, congenital portosystemic vascular anomalies, fulminant hepatic failure, septicemia, and extensive hepatic neoplasia (Center 1996a, 1996b). Glucose intolerance is more common than hypoglycemia in people with severe liver dysfunction. Hyperglucagonemia has been suggested to occur in dogs with cirrhosis that develop an uncommon necrotizing dermatopathy [i.e., superficial necrolytic dermatitis (SND), hepatocutaneous syndrome]. This disorder is characterized by skin erosions and ulcerations with alopecia, exudation, and crusting on the footpads and mucocutaneous junctions (Outerbridge et al. 2002). The mean plasma amino acid concentrations for dogs with SND were significantly lower than for dogs with acute and chronic hepatitis. A metabolic hepatopathy in which there is increased hepatic catabolism of amino acids is hypothesized to explain the hypoaminoacidaemia seen in SND (Outerbridge et al. 2002). (For further discussion on SND, please see Chapter 11).

Protein and Amino Acid Metabolic Alterations

The liver synthesizes the majority of circulating plasma proteins. The most abundant is albumin, which represents 55% to 60% of the total plasma protein pool (Center 1996c). The other proteins synthesized and secreted by the liver are usually glycosylated proteins (i.e., glycoproteins) that function in hemostasis, protease inhibition, transport, and ligand binding. Amino acids can be used for both *de novo* protein synthesis and energy metabolism, and alterations in amino acids are one of the most important metabolic changes in chronic liver failure. Increased muscle breakdown and liver insufficiency induce an increase in the levels of the aromatic amino acids (AAAs) (tyrosine, phenylalanine, tryptophan), and a reduction in those of the branched-chain amino acids (BCAAs) (leucine, isoleucine, valine) Strombeck and Rogers 1978; Dejong et al. 2007). Consistent alterations in the plasma amino acid profiles may suggest a potential role for amino acids in the pathogenesis of hepatic encephalopathy. This characteris-

tic profile of amino acid changes formed the basis for the initial formulation of solutions enriched in BCAAs as a potentially effective nutritional modality for the treatment of chronic liver disease and hepatic encephalopathy (Khanna and Gopalan 2007). In addition, alterations in nitrogen metabolism manifested by hyperammonemia is a common finding and probably results from a combination of factors including active amino acid deamination and gluoconeogenesis, bacterial degradation of protein in the intestine, impaired ureagenesis, and inadequate delivery of ammonia to the liver because of portosystemic vascular shunting (Dimski 1994; Center 1996c). Studies in human patients with liver failure have shown that nitrogen balance can be improved if the diet is divided into small frequent meals, including a snack at bedtime (Swart et al. 1989).

Lipid Metabolic Alterations

After hepatic glycogen stores are depleted, fatty acids are mobilized from adipose tissue, and their rate of hepatic oxidation increases. The release of free fatty acids from adipocytes is greatly accelerated by epinephrine, which stimulates the activation of hormone-sensitive triacylglycerol lipase. Since insulin counterbalances this effect of epinephrine, reduced insulin activity will result in activation of triacylglycerol lipase with consequent hydrolysis of triacylglycerols. The end result is increased release of free fatty acids from adipose tissue into the circulation. Lipoprotein lipase activity is also decreased in liver failure resulting in reduced clearance capacity of exogenous triglycerides. Patients with liver failure can thus be intolerant of large amounts of dietary fat (Barber and Teasley 1984). The liver is also a major site of cholesterol synthesis from acetyl-CoA. Hypocholesterolemia has been recognized in animals with portosystemic vascular anomalies and acquired hepatic insufficiency (Center 1996c), whereas hypercholesterolemia has been seen in animals with obstruction to bile flow.

Vitamin and Mineral Abnormalities

Vitamin deficiencies are commonly found in patients with chronic liver disease. Deficient dietary intake and malabsorption are the principle causes for vitamin deficiency, although decreased storage, metabolism defects, and increased requirements also play a role (Mezey 1978). In human patients with cirrhosis, the hepatic concentrations of folate, riboflavin, nicotinamide (from dietary niacin), pantothenic acid, vitamin B6, vitamin B12, and vitamin A have been found to be decreased (Leevy et al. 1970). The requirements for water-soluble vitamins are determined by the level of caloric intake. With complete anorexia there is a low requirement (Strombeck, Schaeffer et al. 1983), but with resumption of caloric intake, water-soluble vitamins are necessary to replenish coenzymes involved in metabolic processes in the liver and other tissues (Strombeck, Schaeffer et al. 1983). Due to the variety of vitamin deficiencies that may develop and the inability to quantitatively appraise these changes, water-soluble vitamins are empirically supplemented at a doubled daily dose. Subnormal concentrations of vitamin B12 have been demonstrated in some cats with cholangitis and hepatic lipidosis associated with chronic inflammatory bowel disease. Vitamin B12 (cyanocobalamin) can be supplemented parenterally at a dose of 250 µg per cat SQ once weekly for 6 consecutive weeks.

Vitamin C is produced by the liver and lower plasma concentrations of ascorbate are present in dogs and cats with hepatic disease (Strombeck, Harrold et al. 1983). Vitamin C should thus be supplemented, and dogs will tolerate doses of 25 mg/kg body weight PO per day. Malabsorption of fat-soluble vitamins is typically seen in patients with chronic bile-duct occlusion, biliary cirrhosis, end-stage cholangitis, or liver disorders occurring concurrent with pancreatic or intestinal disease causing steatorrhea. Vitamin E may be beneficial for the management of patients with copper-associated liver damage because of its antioxidant effects that protect against lipid peroxidation. Vitamin E should be supplemented at doses of 10–15 IU/kg/day. Caution should be exercised with the administration of vitamin A; however, since this vitamin can interact synergistically with chemicals and endotoxins to injure the liver, despite the use of vitamin A levels that are not normally hepatotoxic (Strombeck, Schaeffer et al. 1983). Vitamin K stores in the liver are limited and can be rapidly depleted when dietary sources are inadequate or lipid malabsorption is severe (Strombeck, Schaeffer et al. 1983). Endogenous production of vitamin K by intestinal bacteria can maintain requirements for 1 month following the lack of dietary supplementation. With bleeding due to hepatic disease, the function for synthesis of the prothrombin-complex clotting factors is always lost before the storage of vitamin K is depleted (Center 1996b, 1996c). Vitamin K deficiency can be diagnosed with a PIVKA (proteins induced by vitamin K antagonism or absence) assay-clotting time. Normalization of prolonged clotting times after parenteral administration of vitamin K1 (0.5–1.0 mg/kg SQ) documents vitamin K deficiency.

There is considerable evidence that zinc deficiency is prevalent in liver disease (Riggio et al. 1991). Urea synthetic capacity is reduced in zinc-deficient patients due to reduced hepatic ornithine transcarbamylase (OTC) activity

and increased muscle glutamine synthetase activity. Zinc deficiency could thus adversely influence multiple aspects of ammonia metabolism (Mullen and Weber 1991), whereas excess zinc inhibits the intestinal absorption of copper and its deposition in the liver (Fisher et al. 1983). Zinc should be orally supplemented as zinc gluconate or zinc citrate (5 mg/kg body weight/day). Hypokalemia is common in human cirrhotic patients, in whom it may be associated with glucose intolerance. Potassium depletion may occur secondary to inadequate dietary intake, vomiting, diarrhea, secondary hyperaldosteronism and use of diuretic drugs. Potassium repletion in these patients is associated with a reversal of subnormal insulin and growth hormone concentrations (Podolsky et al. 1973). Copper hepatotoxicity is a well-documented cause of liver disease in genetically predisposed dogs and can also occur secondary to cholestatic disorders. Secondary copper accumulation rarely exceeds 2,000 ppm (mcg/g) dry weight (dw) in liver tissue (normal < 400 ppm (mcg/g) dw) (Thornburg 2000; Hoffman et al. 2006; Spee et al. 2006).

Malnutrition in Liver Disease

Malnutrition is a common finding in people with advanced liver disease, and has been demonstrated as an independent risk factor for predicting clinical outcome in patients with chronic liver disease (Qiao et al. 1988). It is important to recognize that weight loss commonly occurs in the face of normal dietary intake, suggesting that factors other than caloric intake are involved in the malnutrition of these patients. Significant weight loss occurred in 14% (O'Keefe et al. 1980), mild to moderate steatorrhea in 50%, and deficiency of fat-soluble vitamins occurred in 40% of human patients with nonalcoholic cirrhosis (Morgan et al. 1976). Potential causes of malnutrition in animals with liver disease include: (1) anorexia, nausea, and vomiting; (2) impaired nutrient digestion, absorption, and metabolism; (3) increased energy requirements, and (4) accelerated protein catabolism with impaired protein synthesis.

Prolonged fasting in cirrhosis leads to a rapid consumption of fat stores, and increased gluconeogenesis results in depletion of structural and functional proteins (Munoz 1991). In addition, the chronic administration of lactulose and/or neomycin for hepatic encephalopathy may lead to nutrient malabsorption, secondary to decreased intestinal transit time and suppressed activity of bacterial flora. Cholestatic liver disorders are associated with decreased intraluminal concentration of bile salts resulting in lipid malabsorption and depletion of body fat stores (Kowdley 1998). The steatorrhea that occurs in approximately 40% of human patients with hepatic cirrhosis is related to decreased delivery of bile salts into the intestinal lumen, impaired intestinal capacity for absorption of long-chain fatty acids (Malagelada, Pihl, and Linscher 1974), interference with lipid absorption by neomycin, and in some cases, concurrent exocrine pancreatic insufficiency (Lee and Lai 1976).

NUTRITIONAL MANAGEMENT OF COMMON HEPATOBILIARY DISORDERS

The early identification and resolution of the factors causing hepatic insult is integral to the successful repair and regeneration of the hepatocyte. Nutritional management is frequently delayed in small animal patients with liver disease owing to the insidious onset and lack of understanding of pathophysiologic mechanisms. In addition, therapeutic diets may need to be modified depending on the patient's nutritional status and underlying liver disorder. Sufficient carbohydrate and fat must be provided in the diet to prevent protein catabolism for energy needs and consequent ammonia formation. Although nutritional therapy only plays a supportive role in the management of most hepatic diseases, it is the primary treatment for feline idiopathic hepatic lipidosis and hepatic encephalopathy.

Feline Idiopathic Hepatic Lipidosis

Feline idiopathic hepatic lipidosis (IHL or HL) is a well-recognized syndrome characterized by the accumulation of excess triglycerides in hepatocytes (see Figs. 14.1 and 14.2) with resulting cholestasis and hepatic dysfunction (Biourge, MacDonald et al. 1990). The prognosis for this life-threatening disorder has improved dramatically over

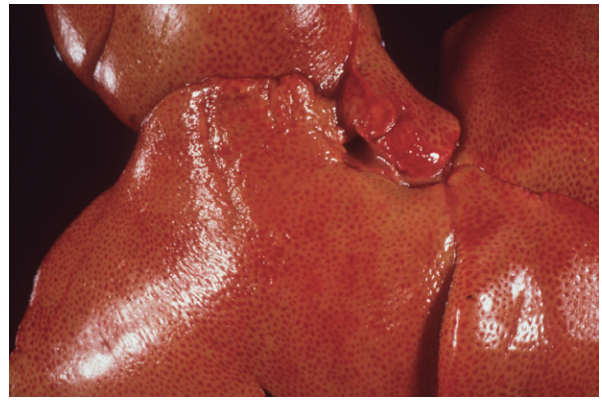

Fig. 14.1. Fatty liver from a cat diagnosed with hepatic lipidosis showing the pale-colored surface, swollen parenchyma, and rounded borders.

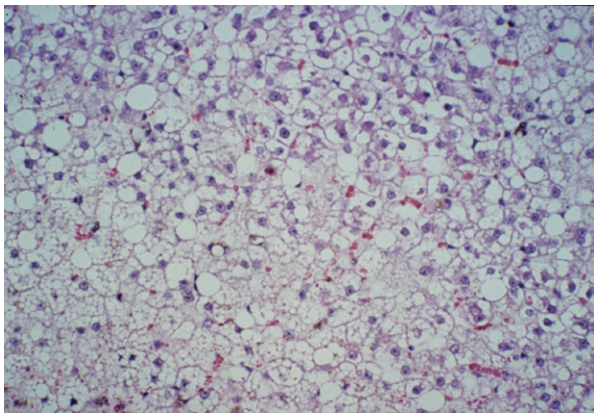

Fig. 14.2. Hepatic biopsy from a cat's liver showing a diffuse vacuolar hepatopathy consistent with hepatic lipidosis.

the past decade as a consequence of the increased utilization of long-term (3 to 8 weeks or longer) enteral feeding devices (Biourge, MacDonald et al. 1990; Biourge, Pion et al. 1993; Center 2005). Despite this progress, the underlying pathophysiology of this syndrome remains incompletely understood. Potential causes include protein deficiency, excessive peripheral lipolysis, excessive lipogenesis, inhibition of lipid oxidation, and inhibition of the synthesis of very-low-density lipoproteins (Center 2005).

Most cats with this disorder are obese and usually present with a history of prolonged anorexia following a stressful event (Biourge, MacDonald et al. 1990; Biourge et al. 1993; Center 2005). Initial management should be directed toward correcting complications such as dehydration, electrolyte abnormalities, hepatic encephalopathy, and infection. Resolution of hepatic lipidosis associated with pancreatitis, infections, and drugs is dependent on the success in treating the underlying disorder (Center 2005). Early tube feeding via esophagostomy or gastrostomy tubes remains the cornerstone of therapy. If the cat cannot be safely anesthetized for placement of an enteral feeding tube, a nasoesophageal tube should be placed, and a liquid, enteral formula should be administered until the cat is stabilized for placement of a longer lasting esophagostomy or gastrostomy tube (please see Chapter 20 for further discussion on enteral feeding).

Energy

Provision of adequate daily energy intake is pivotal for the successful management of cats with HL; however, there are no guidelines for estimated energy needs in cats with HL other than clinical experience. Most cats tolerate feeding to meet their resting energy requirement (RER). This can be increased slightly to 1.1 to 1.2 times RER when the cat is managed at home. Force-feeding is contraindicated because it may be associated with a conditioned food aversion, is stressful for the cat, and is unlikely to provide adequate nutrition. The use of appetite stimulants such as diazepam, oxazepam, cyproheptadine, and mirtazapine can be attempted, but usually results in failure to meet the cat's caloric requirement and frustration for the owner and cat. Caution should be heeded with the use of diazepam in cats with hepatic disease because of the associated fulminant hepatic failure that can ensue (Center, Elston et al. 1996). Esophagostomy and gastrostomy tubes are well tolerated by cats and help ensure the administration of adequate calories. Nasoesophageal tubes have the advantages of relatively low cost and the lack of chemical restraint needed for their placement. Nasoesophageal tubes are a simple and efficient choice for the short-term (less than 10 days) nutritional support of most anorectic hospitalized animals that have a normal nasal cavity, pharynx, esophagus, and stomach (Crowe 1986). Nasoesophageal tube feeding is contraindicated in animals that are vomiting, comatose, or lack a gag reflex. Polyvinylchloride (infant feeding tube, Argyle Division of Sherwood Medical, St. Louis, MO) or red rubber tubes (Robinson catheter, Sherwood Medical, St. Louis, MO) are the least expensive tubes for cats, although the polyvinylchloride tubes may harden within 2 weeks of insertion and cause irritation or ulceration of the pharynx or esophagus. Tubes made of polyurethane (MILA International, Inc., Erlanger, KY) or silicone (Global Veterinary Products, Inc., New Buffalo, MI) are more expensive; however, they are less irritating and more resistant to gastric acid, allowing prolonged usage. A 5 to 8-French tube is more comfortable for cats and smaller dogs.

The tube should terminate in the distal esophagus to decrease the likelihood of reflux esophagitis (Balkany et al. 1977), and this is facilitated by ensuring that the length of the tube approximates the distance from the tip of the nose to the seventh or eighth intercostal space. The small diameter of the tube (5 to 8 French) necessitates the feeding of a liquid enteral formula, and clogging can be a significant problem. Commercially available canned pet foods that are diluted with water will invariably clog the feeding tube. The caloric density of most human and veterinary liquid enteral formulas varies from 1.0 to 2.0 kcal/ml. Diets are fed full strength on continuous (pump infusion) or bolus feeding schedules.

The most common complications associated with the use of nasoesophageal tubes include epistaxis, dacrocystitis, rhinitis, tracheal intubation and secondary pneumonia, and vomiting (Crowe 1986). Vomiting can often be controlled with metoclopramide (0.2 to 0.4 mg/kg) SQ 15 min before each meal. Mild hypokalemia can be treated with oral potassium chloride or potassium gluconate supplementation (5–10 mEq/day with meals).

Protein

Dietary protein should not be restricted in cats with HL unless the cat is showing signs of encephalopathy. Protein restriction for cats with hepatic encephalopathy should not fall below minimum protein requirements. Commercial veterinary diets containing between 25% and 30% protein on an ME basis and 60–68% fat on an ME basis have been well tolerated in most cats with HL that are not encephalopathic (Biourge, Pion et al. 1993). Caution should be heeded in the feeding of human liquid enteral formulas that are typically deficient in the essential amino acids arginine and taurine and contain inadequate levels of protein.

There are a variety of veterinary liquid enteral diets that are marketed for small animal use. These formulas should be fed at room temperature and kept refrigerated between meals. Tube feedings should be started at three to four times daily with a gradual increase in the volume administered. The cat's RER can be met after 4 to 5 days depending on the animal's tolerance to the diet. Commercial canned diets should be blenderized with water to provide a gruel for gastrostomy or esophagostomy tube feeding. The advantages of using a balanced commercial diet is that additional protein, minerals, and vitamins do not need to be added.

Food aversion appears to be an important component of the anorexia of cats with hepatic lipidosis (Biourge 1997). Cats that refuse to eat a diet that they associate with nausea may continue to avoid that diet even after full recovery due to their association with the unpleasant sensation. One should therefore tube feed these cats as soon as the diagnosis of hepatic lipidosis has been made, rather than offer several commercial diets to which the cat can develop an aversion. Cats should not be offered any food by mouth for approximately 10 days following placement of a feeding tube. Cats that express an interest in eating can then be presented with a novel diet that they have not been fed before. The prognosis for HL is influenced to a large degree by the ability of the clinician or owner to aggressively meet the cat's caloric requirements via enteral feeding.

Potassium

Hypokalemia is a relatively common finding in cats with HL and may develop due to inadequate potassium intake, vomiting, magnesium depletion, and concurrent renal failure. In one study, hypokalemia was present in 19 of 66 cats (29%) with severe HL and was significantly related to nonsurvival in this group of cats (Center, Crawford et al. 1993). Hypokalemia is deleterious because it can prolong anorexia and exacerbate hepatic encephalopathy. Diets for cats with HL should be potassium replete (0.8–1% potassium on a DM basis, or 1.5 g/Mcal), or potassium can be orally supplemented at 2 to 6 mEq potassium gluconate per day.

L-Carnitine

Food and biosynthesis by the liver are the primary sources of carnitine for animals. Carnitine is an essential cofactor for transport of long-chain fatty acids across the inner mitochondrial membrane into the mitochondrial matrix for β-oxidation. Carnitine also removes potentially toxic acyl groups from cells and equilibrates ratios of free CoA/acetyl-CoA between the mitochondria and cytoplasm. Several studies have investigated the relationship between carnitine, weight loss in obese cats, and feline hepatic lipidosis. Jacobs et al. (1990) found that mean concentrations of carnitine in plasma, the liver, and skeletal muscle were significantly greater in cats with HL than in control cats. In contrast, other studies have shown that feline diets supplemented with L-carnitine benefit obese cats undergoing rapid weight loss (Center, Harte et al. 2000; Blanchard et al. 2002). In addition, dietary L-carnitine supplementation protected obese cats from hepatic lipid accumulation during caloric restriction and rapid weight loss (Ibrahim et al. 2003). Center and colleagues showed that food supplemented with L-carnitine can safely facilitate rapid weight loss in privately owned obese cats (Center, Harte et al. 2000). Based on these findings, L-carnitine has been recommended for the management of cats with HL at an oral dose of 250 to 500 mg L-carnitine per cat per day. Although there have not been any rigorous placebo-controlled clinical trials evaluating the benefits of L-carnitine in these patients, the clinical impression is one of faster recovery and increased survival rates.

Cyanocobalamin

Cats with HL frequently have inflammatory bowel disease (IBD) or intestinal lymphoma and pancreatitis. Serum concentrations of vitamin B12 are commonly decreased in cats with HL in association with concurrent IBD (Simpson et al. 2001).

Additional dietary supplements that are inconsistently used by some clinicians in cats with severe HL include taurine (250–500 mg/day PO), thiamine (100–200 mg/day PO), and antioxidants such as vitamin E (d-α-tocopherol acetate 10–15 IU/kg/day PO) and SAMe (20 mg/kg/day PO). See the section below for a detailed description of antioxidants for liver disease.

Copper Associated Hepatotoxicity in Dogs

There are three causes of hepatic copper accumulation. A hereditary defect that inhibits biliary excretion of copper, resulting in hepatocellular lysosomal, copper accumulation has been shown to cause the primary form of copper storage disease in humans (Wilson's disease) and Bedlington terrier dogs (Su et al. 1982; Brewer 1998; Thornburg 2000) (see Fig. 14.3). Altered biliary excretion of copper due to hepatic inflammation, fibrosis, and/or cholestasis is suggested to cause secondary copper storage disease, although this has not been proven definitively in the dog (Hoffman et al. 2006; Spee et al. 2006). A third cause of hepatic copper accumulation is from excessive dietary intake (van den Ingh et al. 2007). Absorption of copper is also enhanced by amino acids and high dietary protein, and reduced by zinc, ascorbate, and fiber.

In secondary copper storage disease, copper accumulation is mainly restricted to periportal areas and hepatic copper concentrations are usually less than 2000 ppm (mcg/g) dw (Thornburg 2000; Hoffman et al. 2006). In contrast, copper accumulation with primary hereditary copper storage disorders is always centrilobular, and hepatic copper concentrations are usually greater than 2,000 ppm (mcg/g) dw (Hultgren et al. 1986; Hoffman et al. 2006). Normal hepatic copper concentrations are considered to be less than 400 ppm (mcg/g) dw (Spee et al. 2006; Hoffman et al. 2006).

Breed-associated hepatic copper accumulation with reports of greater than 2,000 ppm (mcg/g) dw has been identified in Bedlington Terriers, West Highland White Terriers, Skye Terriers, Dalmations, Doberman Pinschers, and Labrador Retrievers (see Fig. 14.4; Rolfe and Twedt 1995; Cooper et al. 1997; Haywood et al. 1988; Hoffman et al. 2006; Mandigers et al. 2007). In Bedlington Terriers, copper-associated hepatitis has been identified as an autosomal recessive disease. (Johnson et al. 1980). A deletion in the COMMD1 gene (formerly MURR1) results in reduced biliary excretion of copper and marked accumulation of copper within hepatocytes (Forman et al. 2005). Copper is highly toxic when not bound to protein. In the presence of superoxide ions, copper catalyzes the formation of hydroxyl radicals causing oxidative damage to lipids and proteins, resulting in chronic hepatitis (Forman et al. 2005).

Energy

There are no guidelines for estimated energy needs in dogs with vacuolar, inflammatory, or toxic hepatopathies. Provision of adequate daily energy intake to allow for protein synthesis and prevent tissue catabolism with subsequent ammoniagenesis is important. Most hospitalized dogs are fed at their RER.

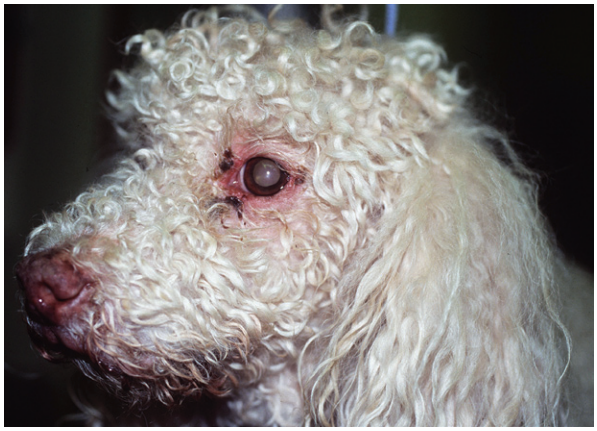

Fig. 14.3. Bedlington Terrier diagnosed with primary copper-associated hepatotoxicity.

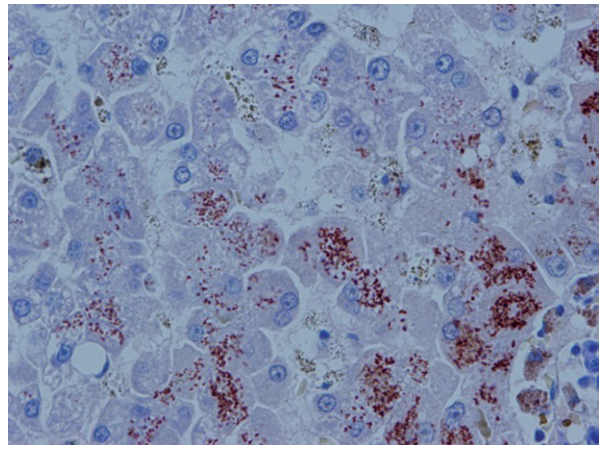

Fig. 14.4. Hepatic biopsy from a Labrador Retriever with chronic hepatitis showing diffuse copper staining (brown pigment) using a Rhodanine stain. (Figure courtesy of Dr. Patricia Pesavento, Department of Pathology, Microbiology, and Immunology, University of California, Davis, School of Veterinary Medicine.)

Dietary Copper Restriction

The management of copper toxicosis is directed at reducing copper stores in the body. Dietary restriction of copper probably plays a minor role in reducing hepatic copper concentrations in diseased dogs (Rolfe and Twedt 1995). Dietary restriction has most potential for managing young dogs affected with an inherited hepatic metabolism defect (Bedlington Terriers and West Highland White Terriers). Commercially available prescription diets are available for dogs and cats with liver disease. These formulations differ from those prescribed for patients with renal disease in that the hepatic formulas are generally less protein-restricted (14–15.5% protein on an ME basis) than most renal diets. In addition, the hepatic diets are restricted in dietary copper, have increased levels of dietary zinc and B vitamins, are moderately restricted in sodium, and are fortified with antioxidants. An alternative option for anorectic dogs that refuse to eat commercial diets or that have concurrent disorders warranting a complex dietary formulation that is not commercially available is to feed a complete and balanced homemade diet that has been formulated by a veterinary nutritionist. Homemade diets should exclude liver, nuts, shellfish, mushrooms, and organ meats that are all high in copper content (Center 1996b). Supplementation of vitamin C is controversial in small animals, with some clinicians preferring to avoid its use because of *in vitro* studies documenting increased transition metal oxidation. In contrast, others advocate a lower dose of vitamin C supplementation (25 mg/kg body weight per day) because plasma ascorbic acid levels can be decreased in dogs with hepatic failure (Strombeck, Schaeffer et al. 1983).

Pharmacologic Reduction of Copper

Copper chelators or zinc therapy are warranted if the liver biopsy of a dog with chronic hepatitis or copper hepatotoxicity shows significant hepatic copper accumulation. Hepatic copper levels >1000 ppm (µg/g) dry weight liver requires therapy to reduce copper concentrations. Animals with >2,000 ppm (µg/g) dry weight copper content should all have chelator therapy for at least 3 months.

Zinc

Zinc salts are effective in preventing copper accumulation in the livers of humans with Wilson's disease (Jaffe et al. 1964). In addition, zinc has antifibrotic and hepatoprotective properties. Zinc ions induce the synthesis of metallothionein, which binds copper tightly, rendering it unabsorbable from the intestine and possibly detoxifying it in the liver (Center, Warner et al. 2002). The copper is lost in the feces when the intestinal cell is sloughed. Zinc acetate or zinc gluconate is recommended, since the sulfate form may be associated with gastric irritation and vomiting in people. An initial induction dose of 15 mg/kg body weight of elemental zinc given twice daily 1 hour before meals is recommended. The dose can be halved after 1 to 3 months of therapy. The goal is to maintain serum zinc concentrations between 200 and 500 µg/dL. The zinc must be administered on an empty stomach and has the common side effect of vomiting. Excess zinc may interfere with the absorption and utilization of iron and copper and can cause a hemolytic anemia (Center 1996b).

Copper Chelators

Copper chelators bind copper either in the blood or tissues and promote its urinary excretion. D-penicillamine (Cuprimine, 250 mg capsules), the most frequent copper chelator recommended for use in dogs, should be given at a dose of 15 mg/kg PO twice a day on an empty stomach (Center 1996b). Anorexia and vomiting are the most common side effects in dogs and can be alleviated by reducing the dose and giving it more frequently. D-penicillamine therapy has also been associated with a pyridoxine deficiency in human patients (Jaffe et al. 1964). Although this problem has not been recognized to occur in dogs, the diet should be high in this B vitamin, or supplemental amounts should be given daily. It is thought that penicillamine induces the production of a hepatic copper-binding protein, metallothionein, thus binding and sequestering copper in a nontoxic form in the liver. A second copper chelator is trientine (Syprine) that has been manufactured for patients that are intolerant to penicillamine. The drug is also administered at a dose of 15 mg/kg PO twice daily on an empty stomach but is better tolerated than penicillamine. Periodic liver biopsies are suggested with the use of copper chelators to monitor hepatic copper levels and response to therapy. Anti-inflammatory agents such as prednisone may be of benefit in the management of chronic hepatitis in Bedlington Terriers and West Highland White Terriers.

Antioxidants

Considerable evidence shows that free radicals are generated in chronic hepatitis and participate in the pathogenesis of oxidative liver injury in dogs and cats. Decreased hepatic glutathione concentrations have been documented in dogs and cats with naturally occurring liver disease (Center, Warner et al. 2002). Normally there is an extensive system of cytosolic and membrane-bound enzymatic and nonenzymatic antioxidants that function to prevent oxidative damage by scavenging or quenching free radicals that are formed.

Vitamin E

Vitamin E (d-α tocopherol) functions as a major membrane bound intracellular antioxidant, protecting membrane phospholipids from peroxidative damage when free radicals are formed. Vitamin E protects against the effects of copper, bile acids, and other hepatotoxins, and is administered at 10–15 IU/kg/day. Because bile acids are required for fat-soluble vitamin E absorption and may be reduced in cholestatic liver disease, a water-soluble formulation is recommended.

S-Adenosylmethionine (SAMe)

S-adenosylmethionine is a precursor of glutathione, an important component of the liver antioxidant system. In a placebo-controlled feline model of oxidant injury from acetaminophen, SAMe-treated cats had reduced Heinz body formation and erythrocyte destruction compared with cats that received acetaminophen alone. Hepatic and blood glutathione concentrations increased with SAMe administration (Webb et al. 2003). There was also evidence of protection in hepatic glutathione (GSH) treated cats. It is important to recognize that there are two well-characterized stereoisomers of the SAMe molecule denoted as "–" SAMe (S,S-SAMe) and "+" SAMe (R,S-SAMe) isomer. This nomenclature refers to the orientation at the sulfonium chiral center. The S,S-SAMe isomer is the predominant form synthesized in cells and is biologically active, whereas <4% of the R,S-SAMe is found in tissues. Both *in vitro* and *in vivo* studies indicate that only the S,S-SAMe isomer has preferential high reactivity with most methyltransferases that have been studied (Beaudouin et al. 1993). SAMe is administered at a dose of 20 mg/kg body weight once daily on an empty stomach (given 1 to 2 hours before feeding). While the stereoisomeric composition of SAMe products is important in determining their biological effects, this information typically is not disclosed for marketed products or may not be known. Recent analysis of Denosyl®, a SAMe product proven to produce biologic responses in healthy dogs and cats and in a canine and feline model of acetaminophen toxicity (Wallace et al. 2002; Webb et al. 2003), demonstrated a 74% content of the biologically active S,S-SAMe stereoisomer, while analysis of another veterinary brand disclosed only a 57% S,S-SAMe isomer content.

Milk Thistle

The active extract of milk thistle is silymarin, which contains four flavonoid stereoisomers; the most biologically potent is silybin. Important functions showing the hepatoprotective properties of silymarin include its role as an antioxidant and free-radical scavenger in the liver. There is also evidence that silymarin has effects in inhibiting hepatotoxin binding, increasing glutathione concentrations and iron chelation, and promoting choleresis (Crocenzi et al. 2003). The oral uptake and bioavailability of silybin is low, but significantly increase when complexed with phosphatidylcholine (Filburn et al. 2007). Milk thistle as silybin or silymarin extract is dosed at 5–15 mg/kg body weight per day orally. To date, limited clinical studies have evaluated the efficacy of silymarin in liver disease in dogs and cats. In one placebo-controlled experimental study of dogs poisoned with the *Amanita phalloides* mushroom, silybin had a significant positive effect on liver damage and survival outcome (Vogel et al. 1984).

Portosystemic Shunts and Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a complex metabolic disorder characterized by abnormal mental status resulting from severe hepatic insufficiency (Bajaj et al. 2009). The syndrome is most often recognized in dogs or cats with congenital anomalies of the portal vascular system (Figs. 14.5, 14.6, and 14.7); however, it may occur in association with chronic progressive hepatic disorders that lead to end-stage liver failure (Fig. 14.8). An understanding of the pathogenesis and precipitating factors for development of HE is integral to successful patient management. The goals of therapy in patients with HE are threefold: (1) early recognition and correction of precipitating causes of

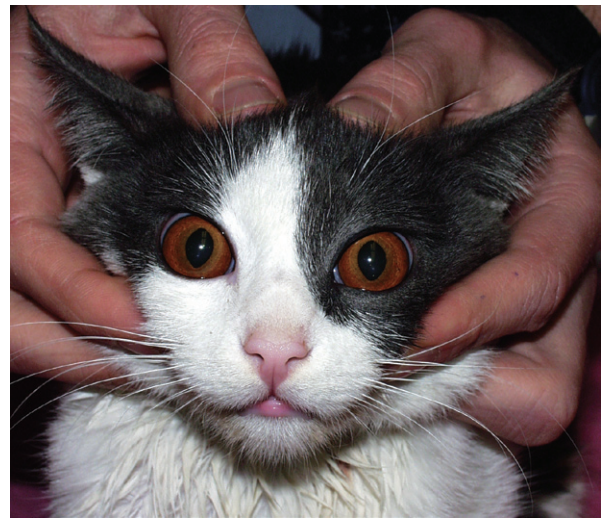

Fig. 14.5. Copper-colored iris in an encephalopathic kitten diagnosed with a portosystemic shunt.

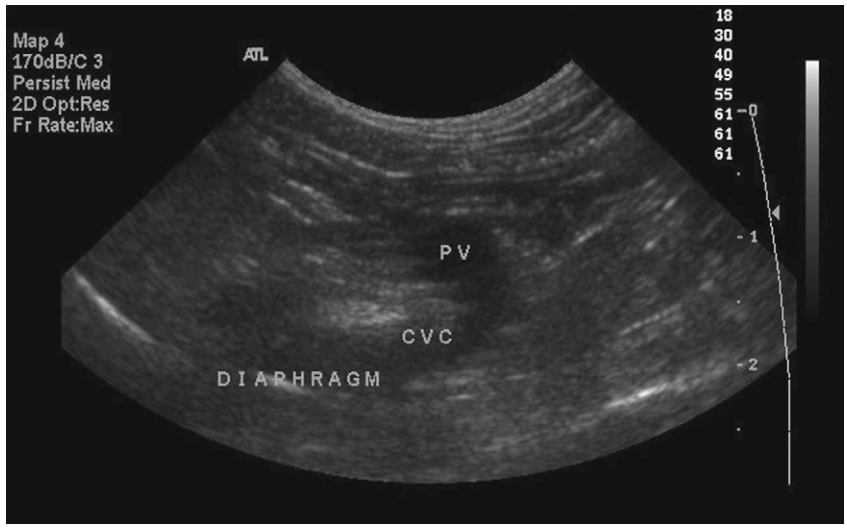

Fig. 14.6. Abdominal ultrasound in a dog with a single extrahepatic portosystemic shunt. PV = portal vein; CVC = caudal vena cava.

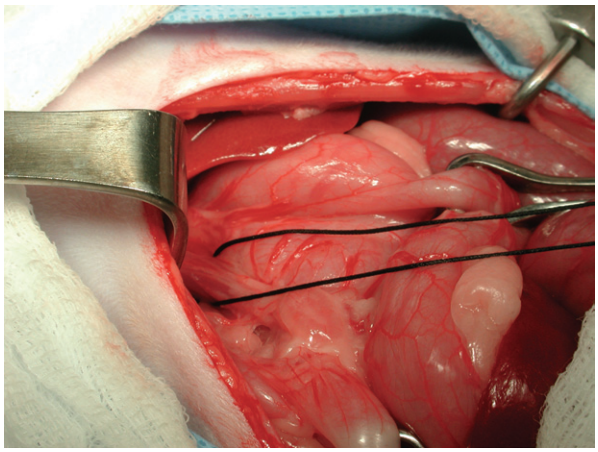

Fig. 14.7. Exploratory laparotomy in a cat with a single extrahepatic shunt showing the ligature around the aberrant vessel.

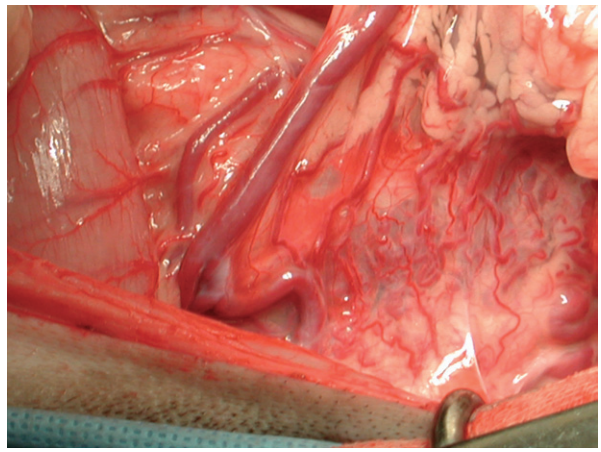

Fig. 14.8. Exploratory laparotomy in a dog showing a plexus of multiple extrahepatic shunt vessels secondary to portal hypertension from hepatic cirrhosis.

encephalopathy (e.g., gastrointestinal bleeding, constipation, hypokalemia); (2) reduction of the intestinal production and absorption of toxins; (3) provision of supportive and symptomatic care. Clinicians should refrain from the use of sedatives, narcotics, and anesthetic agents in patients with HE. Diuretics, in particular furosemide, should be judiciously utilized because overzealous use may cause hypokalemic alkalosis and hypovolemia. Treatments based on the mechanism of intestinal production and absorption of toxins (ammonia, mercaptans, short-chain fatty acids, indoles and skatoles, and biogenic amines) include decreasing or modifying dietary protein, altering intestinal flora, and decreasing intestinal transit time (Center 1996b). Supportive care includes correction of hypovolemia, electrolyte, and acid/base abnormalities (Center 1996b).

Animals with portosystemic shunts (PSSs) and an absence of HE should not be unduly protein restricted.

Instead, efforts should be made to provide normal dietary intake in patients with chronic stable liver disease. Likewise, not all animals with surgically repaired PSSs require protein restriction, and these animals are typically slowly weaned on to normal maintenance diets within 4 to 6 weeks following surgery. Any evidence of dietary protein intolerance on a maintenance diet is usually managed with a moderately protein-restricted diet in the form of commercially manufactured hepatic diets. Alternatively, higher dietary protein levels can be fed in the form of vegetable or milk-based proteins to these animals, with every effort made to avoid the feeding of meat proteins.

Dietary Protein

Protein supplementation remains an enigma of great concern for clinicians caring for patients with HE secondary to hepatic cirrhosis, because these patients may have significantly increased protein requirements (Swart et al. 1988). In contrast, dietary protein should not be restricted in animals with portosystemic shunts (PSSs) that are not encephalopathic, and these animals should be fed as much protein as they will tolerate without becoming clinically encephalopathic. Renal diets are best avoided in animals with liver disease due to the source of dietary protein, and efforts should be made to feed vegetable or dairy proteins if higher levels of protein intake are associated with encephalopathy. Decreased portal venous perfusion or markedly reduced hepatic mass permits encephalogenic material derived from the gut, diet, or endogenous metabolism to spill into the systemic circulation. Subsequent exposure to the blood-brain barrier allows access to the central nervous system (CNS). Nitrogen is normally metabolized to ammonia and detoxified in the hepatic urea cycle. Ingestion of a meat-based high-protein diet, gastrointestinal bleeding, and azotemia are the most common causes of HE in animals with severe liver disease or portosystemic shunting (Center 1996b). The source of protein is critically important in the management of animals with HE. Dogs with experimentally created PSSs had significantly prolonged survival and fewer symptoms of encephalopathy when fed a milk-based diet in contrast to a meat-based diet (Condon 1971). It is possible that heme, RNA, and other nitrogenous bases in the meat-based diet contributed to the exacerbation of hepatic encephalopathy and shortened survival. The presence of diarrhea and soft stools in the dogs receiving the milk-based diet was a possible cause for decreased nitrogen absorption secondary to shortened intestinal transit time and lowering of colonic pH. The latter hypothesis is supported by the finding that encephalopathy is worse in Eck fistula dogs with constipation, and symptoms are reduced following administration of enemas. The benefits of feeding milk proteins are unlikely to be the result of a favorable amino acid composition of the protein's amino acids, because the ratio between the branched-chain and aromatic amino acids is similar for proteins in cottage cheese, meat, and fish. The benefits of cottage cheese are thus likely to be associated with its optimal digestibility and lack of porphyrins such as heme and other nitrogenous bases.

The feeding of vegetable-based diets (soybeans) is also preferred over the feeding of meat-based diets in patients with cirrhosis (Weber, Minco et al. 1985). The effect of vegetable-based diets on nitrogen metabolism can be mainly accounted for by the increased intake of dietary fiber and increased incorporation and elimination of nitrogen in fecal bacteria (Weber, Minco et al. 1985). The benefits of feeding a protein-restricted soy-based diet versus a protein-restricted poultry-based diet to dogs with congenital PSSs were documented when the dogs on the soy-based diet had significantly lower plasma ammonia concentrations compared to the dogs ingesting the poultry-based diet (Proot et al. 2009). Casein-based diets have been fed to both dogs and cats with liver disease; however, these diets have the potential for low arginine concentrations, warranting supplementation of this essential amino acid if administered to cats. Dietary arginine deficiency in otherwise healthy cats can cause hyperammonemia and encephalopathy signs within 30 minutes of consumption of a high protein diet (Morris 1985).

Parenteral or enteral supplemental formulas containing reduced AAAs and increased BCAAs designed to normalize circulating amino acids have been evaluated in a number of clinical trials of portal systemic encephalopathy. Despite the large number of investigations, it is difficult to analyze the data because of marked differences in the study designs, lack of randomization, and the varying formulas utilized (Wahren et al. 1983; Cerra, Cheung et al. 1985; Michel et al. 1985). Meta-analysis of these studies by two different groups gave diametrically opposite results. Although BCAAs may be effective in restoring positive nitrogen balance, they do not appear therapeutically effective in either acute or chronic HE. In addition, BCAA supplementation is extremely expensive (Morgan 1990).

Protein-restricted renal and hepatic diets are recommended for cats and dogs with hepatic encephalopathy, although there are as yet no published studies demonstrating the benefits of these diets for liver disease. Renal diets are not optimal for the management of hepatic encephalopathy due to the large quantities of organ meats in some

of these diets. Homemade diets that avoid the use of meat-based protein sources can be used as effective alternatives to commercial diets. Fat- and water-soluble vitamins should be supplemented in the diet. Zinc should also be supplemented since depletion of this mineral has been suggested as a precipitant of HE in people with liver failure (van Der Rijt et al. 1991). In addition, the administration of zinc has induced psychomotor improvements in patients with mild HE (Reding et al. 1984).

Management of animals with urate stones in the bladder secondary to PSS remains a challenge for clinicians, as these stones are not amenable to dissolution with dietary intervention. These stones are typically removed surgically via cystotomy or with lithotripsy (see Chapter 16).

Nonabsorbable Disaccharides

Lactulose administration is considered to be one of the treatments of choice in hepatic encephalopathy. It is a synthetic disaccharide that is hydrolyzed by colonic bacteria, principally to lactic and acetic acids (Lieberthal 1988). Lactulose appears to exert its beneficial effects by: (1) Lowering colonic pH with subsequent trapping of ammonium ions; (2) inhibiting ammonia generation by colonic bacteria through a process known as catabolite repression; (3) decreasing intestinal transit time due to its cathartic properties; and (4) suppressing bacterial and intestinal ammonia generation by providing a carbohydrate source. The dose to achieve these goals is somewhat variable, although most dogs and cats can be managed with lactulose at 0.25–0.5 mg/kg body weight PO q 8 to q 12 hours. The dose should be reduced if watery diarrhea develops. Lactulose is also highly effective when added to enema fluid (30% lactulose, 70% water) and given as a retention enema. Approximately 20–30 ml/kg body weight of this lactulose enema solution is infused and retained in the colon for 20 to 30 min before evacuation. Lactulose requires intestinal bacteria to be activated; however, neomycin and other antibiotics inhibit bacterial growth. Despite this antagonism, the two agents have been used simultaneously with additive or synergistic effects (Weber, Fresard et al. 1982).

Antimicrobials

A number of antimicrobials have been advocated for use in patients with portosystemic encephalopathy. Most drugs effective in this capacity are inhibitory to the urease-producing bacteria that frequently comprise gram-negative anaerobic bacteria. Administration of ampicillin or neomycin appear to provide short-term clinical benefit in both dogs and cats with acute HE associated with portosystemic vascular anomalies. Cats demonstrating ptyalism as a sign of HE appear particularly responsive to ampicillin, fluid therapy, and temporary withdrawal of food. Although metronidazole has broad-spectrum activity against enteric anaerobes such as *Bacteroides* spp. that are believed to metabolize nitrogenous dietary substances, it should be avoided in patients with HE due to its adverse effects (i.e., ataxia, seizures, anorexia) that can mimic manifestations of HE.

Chronic Hepatitis

Chronic hepatitis is a poorly defined clinicopathologic entity characterized by parenchymal necrosis, particularly piecemeal necrosis, with associated lymphocytic inflammation (Thornburg 1982). The disease can have an insidious onset, contributing to the poor understanding of its etiopathogenesis and advanced stage when recognized. Nutritional management is thus frequently delayed and is directed at arresting inflammation, correcting nutritional derangements, and resolving fibrosis. Specific therapy involves the use of immunomodulatory drugs such as corticosteroids (with or without azathioprine), choleretics such as ursodeoxycholic acid (Meyer et al. 1997), copper chelators (if warranted based on copper quantitation of liver biopsies), zinc, and antioxidants such as SAMe and vitamin E. Protein intake should not be restricted in these animals unless the patient shows signs of protein intolerance. The principles of nutritional support are similar to those for the patient with copper-associated hepatotoxicity although copper does not need to be restricted unless warranted based on a liver biopsy.

Parenteral nutrition offers the possibility of increasing or ensuring nutrient intake in patients in whom sufficient nutrition by the oral or enteral route alone is insufficient or impossible. Parenteral nutrition should be considered in patients with acute hepatotoxicity with subsequent HE in which enteral feeding is either contraindicated or not tolerated by the patient. Total parenteral administration (central parenteral administration) to dogs and cats with chronic hepatitis and cholangitis was associated with a mortality rate of approximately 50% (Reuter et al. 1998; Pyle et al. 2004). The relatively high mortality rate was more likely a reflection of the increased selection of critically ill patients unable to tolerate enteral nutritional support and whose prognosis was unaltered or worsened with the advent of total parenteral nutrition support.

Ascites should be managed with dietary sodium restriction and judicious use of diuretics. Commercially available hepatic diets are sodium restricted and are recommended. Homemade diets can also be prepared with replacement of

iodized salt (NaCl) with potassium chloride. Spirinolactone, administered at 1 to 2 mg/kg PO twice daily, is the diuretic of choice since it blocks the action of aldosterone at the distal renal tubules and collecting ducts (Boyer and Warnock 1983). Diuretics must be used cautiously to prevent dehydration and hypovolemia, with secondary exacerbation of HE. In addition, corticosteroids are catabolic to body proteins and could precipitate a worsening of clinical signs caused by the increased ammonia production.

SUMMARY

- The specific nutritional requirements of dogs and cats with liver disease have not been well defined to date.
- The underlying cause of liver disease should be identified and treated whenever feasible.
- Dietary protein should not be restricted in nonencephalopathic animals with liver disease, including PSSs.
- Highly digestible vegetable-based and milk proteins are better tolerated than animal proteins in animals with hepatic encephalopathy.
- Anorexia is a common manifestation of liver disease and adequate energy and nutrient intake can easily be facilitated with the use of enteral feeding devices.
- Early nutritional support with nasoesophageal, esophagostomy, or gastrostomy tubes remains the cornerstone of therapy for cats with hepatic lipidosis.
- There is increasing evidence that liver support in the form of supplementation with antioxidants (SAMe, milk thistle, vitamin E) has a hepatoprotective role, particularly in inflammatory hepatopathies.

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Nutritional Management of Kidney Disease

15

Denise A. Elliott

CHRONIC KIDNEY DISEASE

Dietary therapy has remained at the forefront of the management of chronic kidney disease for decades. There are two fundamental applications of nutrition in chronic kidney disease: the first is the key role that certain nutrients have in altering disease progression, and the second is the role of nutrition in controlling uremic symptoms and improving the quality of life.

Water

Compensatory polydipsia balances excessive fluid loss associated with osmotically driven polyuria; however, some patients will fail to consume sufficient water to prevent volume depletion. Therefore, methods should be employed that encourage the patient to drink and maintain fluid balance. An increase in water turnover can be achieved by feeding diets that contain 70–85% moisture (can, pouch, tray), by increasing feeding frequency (increasing number of meals per day), or by adding water to the diet (Dumon et al. 1999; Kirschvink et al. 2005). The pet should have easy access to fresh water at all times. Providing water at several locations in the house may facilitate water intake. The water bowl should be kept full at all times, and it must be clean so that the pet is not turned off by odors from the bowl. Cats have very sensitive whiskers and many seem to prefer a large bowl in which the whiskers do not touch the sides of the bowl. A variety of water types (home-filtered, distilled, bottled, warm tap water, cold tap water) can be offered. Some pets prefer running water, and water fountains are now commercially available to encourage water intake. It is important to keep the food and water bowls away from the litter box area.

When fluid balance cannot be maintained with the above techniques, cautious fluid supplementation should be used to prevent dehydration and attendant vascular depletion. Maintenance fluids (e.g., Plasma-Lyte 56, Plasma-Lyte M, Normosol M) can be administered subcutaneously daily by the pet's caretaker. Chronic administration of Lactated Ringer's solution or sodium chloride will cause hypernatremia due to failure to provide sufficient free water. Conversely, 5% dextrose in water is hypotonic and should not be administered subcutaneously.

Energy

Sufficient energy needs to be provided to prevent endogenous protein catabolism that will result in malnutrition and exacerbation of azotemia. Prevention of malnutrition by ensuring adequate energy and nutrient intake is crucial in the management of kidney disease. The maintenance energy requirements are a good starting point to determine the amount of calories required each day. Commonly used equations indicate adult cats require 50–70 kcal/kg/day, and dogs require $130 \times \text{BW (Kg)}^{0.75}$ (see Chapter 3). This starting point should be adjusted based on serial determinations of body weight and body condition score. Carbohydrate and fat provide the nonprotein sources of energy in the diet. Fat provides approximately twice the energy per gram compared to carbohydrate. Therefore, fat increases the energy density of the diet, which allows the patient to obtain its nutritional requirements from a smaller

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volume of food. A smaller volume of food minimizes gastric distention, which reduces the likelihood of nausea and vomiting.

Protein

Dietary protein modification has been a mainstay for the management of chronic kidney disease for decades. However, over the years dietary protein restriction has also been the subject of much controversy. It is clearly helpful to consider dietary protein intake within two different contexts; implementation in stage I/II disease (IRIS 2006) with the primary aim of altering disease progression and implementation in stage III/IV disease to control uremic symptoms.

Stage I/II: Progression

The intact nephron hypothesis is the prevailing theory of the progression of renal disease (Hostetter et al. 1981). In this model, once a critical threshold of functioning nephrons is reached, the remaining surviving nephrons hypertrophy and undergo an increase in the glomerular plasma flow and glomerular filtration rate. The capillary blood flow and the pressure gradient across the capillary wall increase, and the chemical and electrical selective glomerular barrier are impaired. These changes result in increased amounts of protein entering the glomerular filtrate. Ultimately the tubular resorptive processes for protein are overwhelmed. The tubular cells are stimulated to secrete cytokines and inflammatory mediators including endothelin-1, monocyte chemotractant protein-1 (MCP-1), and RANTES (regulated on activation, normal T-cell expressed and secreted; also known as CCL5, chemokine ligand 5) that stimulate interstitial fibrosis and inflammation which contribute to progressive renal damage (Remuzzi and Bertani 1998). Accordingly, protein restriction has been demonstrated to slow the rate of progression of renal disease in rats and people by reducing renal blood flow, glomerular filtration rate, and proteinuria.

It is less certain if protein restriction alters progression of renal failure in dogs or cats (Adams, Polzin, Osborne et al. 1993; Finco, Brown, Brown et al. 1999; Finco, Brown, Brown et al. 1998; Finco Brown, Crowell et al. 1994; Finco, Brown, Crowell et al. 1992a, 1992b; Finco, Crowell et al. 1985; Polzin, Leininger et al. 1988; Robertson et al. 1986). Most studies have been performed using the remnant kidney model, which does not necessarily reflect naturally occurring disease. In addition, some of the studies have been confounded by alterations in energy and/or phosphate intake in addition to protein restriction. Brown et al. reported that protein restriction did not alleviate glomerular hypertension, hypertrophy, hyperfiltration, or progression in dogs with induced renal failure (Brown, Finco, Crowell et al. 1990; Brown, Crowell, Barsanti et al. 1991).

Recent research suggests that the urine protein-to-creatinine ratio (UPC) is an independent risk factor for all-cause mortality of cats with naturally occurring chronic kidney disease, cats with systemic hypertension, and uremic crisis (Jepson et al. 2007; King, Gunn-Moore et al. 2006; Kuwahara et al. 2006; Syme, Markwell et al. 2006; King, Tasker et al. 2007). Furthermore, a study in dogs with naturally occurring chronic kidney disease has reported that a UPC value greater than 1 at initial evaluation is associated with an increased risk of uremic morbidity and mortality, and the risk of adverse outcomes increases as the magnitude of proteinuria increases (Jacob, Polzin, Osborne et al. 2005). As proteinuria is a significant independent risk factor for reduced survival in cats and dogs with naturally occurring chronic kidney disease, therapeutic strategies should be employed to minimize proteinuria (Lees et al. 2005). Angiotensin converting enzyme (ACE) inhibitor therapy has been shown to reduce glomerular capillary pressure and to lower the UPC (King et al. 2006; Grauer et al. 2000).

As a result of these new research findings, there is now renewed interested in the role, if any, of protein restriction on proteinuria and the progression of chronic kidney disease. The effect of dietary protein restriction on proteinuria in dogs and cats with chronic kidney disease is not clear. Initial studies in feline remnant kidney models suggested a beneficial effect of protein restriction on the development of glomerular lesions (Adams, Polzin, Osborne et al. 1993; Adams, Polzin, Osborne et al. 1994). However, the results of these studies were confounded by alterations in both protein and energy intake. A subsequent study by Finco et al. failed to demonstrate a benefit of protein restriction on renal lesions (Finco, Brown, Brown et al. 1998). There have not been any reports on the effect of dietary protein restriction and proteinuria in dogs with chronic kidney disease. However, studies have reported that high dietary protein intake increased the magnitude of proteinuria in dogs with laboratory induced kidney disease (Polzin and Osborne 1988). Therefore, it seems logical that restricting protein intake would limit feeding-related hyperfiltration. It is clear that further studies are required to evaluate the effect of protein restriction on proteinuria and progression in dogs and cats with naturally occurring chronic kidney disease.

The International Renal Interest Society (IRIS) recommends implementation of a restricted protein diet in con-

junction with ACE inhibitors for dogs in stage I kidney disease with a UPC > 2 and for dogs in stage II to IV disease, with a UPC > 0.5 (IRIS 2006). Dietary protein restriction in conjunction with ACE inhibitors is recommend for cats with stage I disease who have a UPC > 2, whereas the intervention point for treatment of cats with stage II to IV disease is a UPC > 0.4.

Stage III/IV: Uremia

Azotemia and uremia are due to the accumulation of protein metabolites derived from excessive dietary protein and degradation of endogenous protein. High protein intake exacerbates the azotemia and morbidity of chronic renal failure, while protein malnutrition is strongly correlated with morbidity and mortality (Polzin, Osborne et al. 1983).

The rationale for formulating a diet that contains a reduced quantity of high-quality protein is based on the premise that controlled reduction of nonessential amino acids results in decreased production of nitrogenous wastes with consequent amelioration or elimination of clinical signs, even though renal function remains essentially unchanged. Studies have clearly shown that modifying dietary protein intake can reduce blood urea nitrogen and provide clinical benefits to dogs and cats with chronic kidney disease (Finco, Crowell et al. 1985; Hansen et al. 1992; Jacob, Polzin, Osborne et al. 2002; Leibetseder and Neufeld 1991; Polzin, Leininger et al. 1988; Polzin and Osborne 1988; Polzin, Osborne, Stevens et al. 1983). Therefore, every patient symptomatic for stage III/IV chronic kidney disease should benefit from a protein-restricted diet. The minimal dietary protein requirements of dogs and cats with chronic kidney disease are not known but are presumed to be similar to the minimal protein requirements of healthy animals, i.e., for dogs: 2.62 g/kg $BW^{0.75}$ or 20 g/Mcal, and for cats: 3.97 g/kg $BW^{0.67}$ or 40 g/Mcal (NRC 2006). However, this degree of restriction is necessary only in pets with profound uremia, and more liberal levels can be fed to patients with greater renal function.

The dietary protein level should be adjusted to minimize excesses resulting in azotemia while simultaneously avoiding excessive restriction because of the risk of protein malnutrition. Most pets have minimal clinical signs when the blood urea nitrogen is less than 80 mg/dL. If evidence of protein malnutrition occurs (i.e., hypoalbuminemia, anemia, weight loss, or loss of muscle mass), dietary protein should be gradually increased until these abnormalities are corrected. High-quality protein sources must be used in the formulation of restricted-protein diets to minimize the risks of essential amino acid deficiency.

Dietary protein restriction can have additional benefits in amelioration of the clinical signs associated with chronic kidney disease. Modified protein diets can help to diminish the magnitude of polyuria and polydipsia because less solute is delivered to the kidneys in the form of proteinaceous waste products. The magnitude of anemia may also be reduced, as nitrogenous waste products have been incriminated in hemolysis, shortened red blood cell survival, and blood loss by gastrointestinal ulcerations and impaired platelet function.

IRIS recommends implementation of a restricted-protein diet to decrease azotemia in dogs and cats with stage III/IV disease (IRIS 2006).

Phosphate

Phosphate retention is one of the most common regulatory derangements of chronic kidney disease that arises secondary to reduced glomerular filtration of phosphorus. Phosphate retention and hyperphosphatemia occur early in chronic kidney disease and play key roles in the genesis and progression of renal secondary hyperparathyroidism, hypocalcemia, renal osteodystrophy, and relative or absolute deficiency of 1,25-dihydroxyvitamin D (Barber and Elliott 1998; Nagode and Chew 1992). Soft tissue mineralization develops as the calcium-phosphate product (concentrations expressed in mg/dL) exceeds 60. Renal mineralization will promote interstitial inflammation, fibrosis, and may contribute to progressive renal damage (Nagode and Chew, 1992).

The initial increase in both intracellular and plasma phosphate concentration triggers parathyroid hormone (PTH) synthesis and secretion. PTH works at the level of the proximal tubule to decrease phosphate reabsorption and so increasing excretion of phosphate, which compensates for the reduced glomerular filtration of phosphorus. However, the increased PTH concentrations also trigger the release of phosphate from bone, which contributes to hyperphosphatemia. With progression of the kidney disease, the increased PTH concentrations are counterproductive, contributing to calcitriol deficiency and hypocalemia. Calcitriol production is regulated by 1-α-hydroxylase in the kidney. The activity of 1-α-hydroxylase decreases as a result of loss of functional renal mass and hyperphosphatemia. Calcitriol deficiency reduces the intestinal absorption of calcium, reduces the release of calcium and phosphate from bone, reduces the renal reabsorption of calcium and phosphate, and increases the synthesis and release of parathyroid hormone.

Studies have clearly shown that by minimizing hyperphosphatemia, secondary hyperparathyroidism and its

sequela can be prevented (Barber et al. 1999; Nagode and Chew 1992; Finco, Brown, Crowell et al. 1992b; Ross, Finco et al. 1982; Brown, Crowell, Barsanti et al. 1991). In one study of dogs with surgically induced reduced renal function, dogs fed a low-phosphorus diet (0.44% DM) for 24 months had a 75% survival versus a 33% survival in dogs fed a high-phosphorus diet (1.44% DM) (Finco, Brown, Crowell et al. 1992b). Renal function also deteriorated more rapidly in the high-phosphorus group. Ross et al. reported that cats with laboratory-induced reduced renal mass that were fed a phosphorus-restricted diet (0.24% DM) showed little or no histological change compared with cats fed a "typical" diet containing 1.56% DM phosphorus. The cats in the normal dietary phosphate group had evidence of mineralization, fibrosis, and mononuclear cell infiltration in the renal tissue (Ross, Finco et al. 1982). The efficacy of dietary phosphate restriction in cats with naturally occurring chronic kidney disease has also been published. Dietary phosphate restriction is clearly associated with a reduction in both plasma phosphate and parathyroid hormone concentration (Barber, Rawlings et al. 1999). Furthermore, control of phosphate concentrations has been associated with a reduction in all-cause mortality in cats with naturally occurring chronic kidney disease (Elliott, Rawlings et al. 2000). The mechanism of how phosphate restriction slows progression of renal disease is not fully understood. It may be related to decreased phosphate retention, decreased soft tissue mineralization, prevention of secondary hyperparathyroidism, or most likely, a combination of these factors.

The clinical importance of dietary phosphate control in cats with naturally occurring chronic kidney disease has clearly been reported in a retrospective study of 211 cats by Boyd et al. (2008). In that study, each 1-unit increase (in mg/dL) in the phosphorus concentration was associated with an 11.8% increased risk of death.

The first step to control plasma phosphate concentration is to limit the dietary intake of phosphate. The plasma phosphate concentration should be reassessed within 2 weeks of implementing dietary restriction. If dietary restriction is not effective in controlling the plasma phosphate concentration, intestinal phosphate binders should be added to the treatment plan. Intestinal phosphate binding agents combine with phosphate contained in dietary and digestive secretions to form insoluble complexes that are excreted in the feces. They should be mixed with the food prior to feeding to ensure maximal phosphate binding effectiveness. The plasma phosphate concentration should continue to be monitored every 2 to 4 weeks, and dosage adjustments made accordingly until the target phosphate concentration is achieved. IRIS recommends that the phosphate concentration should be maintained at 2.7–4.5 mg/dl for stage II; < 5 mg/dl for stage III, and < 6 mg/dl for stage IV disease.

Calcitriol replacement therapy has been advocated by some authors to help limit renal secondary hyperparathyroidism (Nagode, Chew et al. 1996). The serum phosphate concentration should be within the reference range prior to beginning therapy, and hyperparathyroidism should be confirmed by parathyroid hormone concentration measurement. Calcitriol should not be given with meals because it enhances intestinal calcium and phosphate absorption. Serum calcium and phosphate concentrations need to be continuously monitored to avoid hypercalcemia and soft tissue mineralization. The risk of hypercalcemia is heightened by the concurrent administration of calcium-based intestinal phosphate binding agents. The serum PTH concentration should return to normal or almost normal within several weeks of initiating therapy.

Electrolytes

Sodium

Sodium restriction has historically been recommended for patients with chronic kidney disease. The rationale was based on the reduced ability of the remaining nephrons to excrete sodium, and the concern that whole body sodium accumulation would contribute to the development of hypertension. Hypertension is indeed common in chronic kidney disease and has been implicated as a factor that contributes to the progression of chronic kidney disease. Approximately 20% of cats with naturally occurring chronic kidney disease have arterial blood pressures > 175 mmHg, which places them at severe risk of target organ (i.e., kidney, eye, brain, heart) damage secondary to hypertension (Syme, Barber et al. 2002). However, blood pressure is not higher in cats with more severe chronic kidney disease (Syme, Barber et al. 2002). Furthermore, blood pressure increases gradually over time in cats with naturally occurring chronic kidney disease, but this is not associated with a decline in kidney function (Syme 2003). Jacob et al. reported that 31% of dogs with naturally occurring chronic kidney disease had systolic blood pressure > 160 mmHg (Jacob, Polzin, Osborne et al. 2003). Dogs with naturally occurring chronic kidney disease and a systolic blood pressure greater than 180 mmHg were more likely to develop a uremic crisis and to die compared with dogs that have a normal systolic blood pressure (Jacob, Polzin, Osborne et al. 2003). Furthermore, the risk of developing a uremic crisis and of dying increased significantly as systolic blood pressure increased.

There have not been any published studies to demonstrate that sodium restriction will alleviate hypertension or slow disease progression. Altering sodium intake from 0.5 to 3.25 g Na/Mcal did not influence the development of hypertension nor affect glomerular filtration rate in dogs with surgically induced renal reduction (Greco, Lees, Dzendzel et al. 1994a, 1994b). A study in cats with surgically induced kidney disease reported that sodium restriction (0.5 g/Mcal) activated the renin-angiotensin-aldosterone system, significantly lowered plasma potassium concentration, and had no effect on arterial blood pressure (Buranakarl et al. 2004). Hanson et al. reported that changes in dietary sodium intake did not affect blood pressure in nine dogs with naturally occurring chronic kidney disease (Hansen et al. 1992). Syme (2003) reported that systolic blood pressure did not change following the introduction of a sodium-restricted renal care diet to cats with naturally occurring chronic kidney disease. Plasma aldosterone concentration and plasma renin activity were higher when cats were consuming a sodium-restricted renal diet. Consistent with IRIS recommendations, there is currently no evidence to suggest that lowering dietary sodium will reduce blood pressure in dogs or cats with chronic kidney disease. However, antihypertensive therapy is clearly recommended to maintain the systolic blood pressure < 160 mmHg in dogs and cats with chronic kidney disease (IRIS 2006).

Potassium

Hypokalemia has been well recognized for decades as a complication of chronic kidney disease. The mechanism of action is unclear and includes inadequate potassium intake, acidifying diets, or increased urinary losses. Hypokalemia occurs in about 20% of cats with chronic kidney disease, although this number may underestimate the true prevalence of whole body potassium depletion (DiBartola, Rutgers et al. 1987; Theisen et al. 1997). Hypokalemia can occur at any stage of disease. Elliott and Syme (2003) reported hypokalemia in 14.3% of cats with stage II, 25% of cats with stage III and 30% of cats in stage IV disease. Segev et al. (2010) reported that hypokalemia occurred in 14% of dogs with naturally occurring chronic kidney disease.

Questions have also been raised regarding hypokalemia as a cause or a consequence of feline chronic kidney disease (Dow and Fettman 1992). An association between chronic kidney disease and hypokalemia has been reported in cats (Dow, Fettman et al. 1989). Furthermore, feeding an acidifying or potassium deplete diet has been associated with naturally occurring chronic kidney disease and a decline in glomerular filtration rate (DiBartola, Buffington et al. 1993; Dow, Fettman et al. 1990; Dow, Lecouteur et al. 1987). Dow and Fettman (1992) hypothesized that potassium depletion may lead to a self-perpetuating cycle of renal damage and further potassium loss. However, the causal relationship between whole body potassium deficit and progressive renal injury remains to be proven.

Clinically, hypokalemia is generally mild without overt clinical signs. Hypokalemia causes generalized muscle weakness and pain that may present as cervical ventroflexion and a stiff, stilted gait (Dow, Lecouteur et al. 1987). Hypokalemia impairs protein synthesis, promotes weight loss, and contributes to polyuria by decreasing the renal responsiveness to ADH (antidiuretic hormone). Hypokalemia also appears to be associated with an increased risk of systemic hypertension in cats with chronic kidney disease (Syme, Barber et al. 2002).

Potassium supplementation is indicated when the serum potassium concentration is less than 4 mEq/L. This may be achieved by oral potassium gluconate or potassium citrate supplementation. Potassium chloride can be acidifying and therefore counterproductive in chronic kidney disease. Clinical improvement in appetite and activity level has been noted following potassium supplementation. Muscle weakness typically resolves within 5 days of institution of therapy. However, a randomized controlled clinical trial failed to identify any beneficial effect of potassium gluconate supplementation on blood pressure or kidney function in cats with naturally occurring chronic kidney disease (Elliott and Syme 2003). Side effects of potassium supplementation include gastrointestinal irritation, ulceration, nausea, and vomiting. The potassium dosage should be adjusted by monitoring the serum potassium concentration and response to supplementation.

It is important to note that not all cats with chronic kidney disease are hypokalemic. Indeed, one study of 116 cats reported that 13% of cats with chronic kidney disease were hyperkalemic (Dow, Fettman et al., 1989). Segev et al. (2010) reported that 71 of 152 (41%) of dogs with naturally occurring chronic kidney disease had at least one reported episode of hyperkalemia, defined as a serum potassium concentration above the reference range of 5.3 mmol/L. Furthermore, 16% of dogs had at least one episode in which the serum potassium concentration was greater than 6.5 mmol/L. Postulated contributors to hyperkalemia include advanced kidney disease, dietary potassium intake, and the concurrent use of medications such as angiotensin converting inhibitors.

Management of hyperkalemia includes ruling out contributory factors such as thrombocytosis and medications.

A complete dietary history including treats and nutritional supplements should be obtained to ascertain the patient's daily potassium intake. This information is used to identify and implement a dietary regime that would provide less dietary potassium. It is important to note that hyperkalemia can occur in dogs with naturally occurring chronic kidney disease that receive therapeutic renal diets (Segev et al. 2010). In this situation, a potassium-reduced, home-prepared diet should be specifically formulated for the patient by a board-certified veterinary nutritionist.

Acid Base Balance

The kidneys are essential in the regulation of acid base balance. One of their key roles is to excrete metabolically derived nonvolatile acid (e.g., sulfates, hydrogen ions). As renal function declines, the capacity to excrete hydrogen ions and reabsorb bicarbonate ions is lost and metabolic acidosis ensues. Metabolic acidosis results in increased renal ammoniagenesis, which has been associated with activation of complement and may contribute to the progression of kidney disease. Metabolic acidosis increases the catabolism and degradation of skeletal muscle protein, disrupts intracellular metabolism, and promotes dissolution of bone mineral. These cellular disruptions exacerbate azotemia, contribute to the loss of lean body mass, and promote renal osteodystrophy. Metabolic acidosis also increases the likelihood that hypokalemia will occur or exacerbates pre-existing hypokalemia as potassium moves out of the cells in response to metabolic acidosis and is lost in urine.

Metabolic acidosis is typically evident in stage III to IV disease (Elliott, Syme, and Marwell 2003). Dibartola et al. reported that 62.7% of cats with chronic kidney disease had a bicarbonate concentration <15 mmol/L (DiBartola, Rutgers et al. 1987). A more recent study of 59 cats with naturally occurring chronic kidney disease reported that 15% of cats with late stage III and 52.6% of cats with stage IV chronic kidney disease had evidence of acidosis (Elliott, Syme, Reubens et al. 2003).

The blood bicarbonate concentration should be maintained in the range of 18–24 mmol/L. Therefore, alkalinization therapy (e.g., potassium citrate, sodium bicarbonate, calcium carbonate) should be implemented when the bicarbonate concentration is < 18 mmol/L. Dietary protein restriction results in the consumption of reduced quantities of protein-derived acid precursors; however, this alone is rarely adequate to prevent metabolic acidosis. The choice and dose of bicarbonate supplementation will need to be individualized for each patient. Factors to consider include the effect on palatability when added to the diet, the presence of hypokalemia (where potassium salts will be chosen), the presence of hyperphosphatemia (calcium salts may be considered because of their phosphate binding capabilities provided hypercalcemia does not occur), and the concurrent presence of congestive heart failure (sodium salts may contribute to fluid overload).

Alkalinization therapy will improve the clinical signs of anorexia, lethargy, nausea, vomiting, muscle weakness, and weight loss in addition to limiting the catabolic effects of metabolic acidosis on protein metabolism. It remains to be determined if there is any beneficial effect to provide alkali supplementation prior to the detection of metabolic acidosis.

Long-Chain Omega-3 Fatty Acids

Long-chain omega-3 fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] compete with arachadonic acid (AA) and alter eicosanoid, thromboxane, and leukotriene production (Bauer et al. 1999). Studies in laboratory-induced renal disease in dogs have reported that supplementation with menhaden fish oil (rich in omega-3 polyunsaturated fatty acids) was considered to be renoprotective compared with safflower oil (rich in omega-6 polyunsaturated fatty acids) and beef tallow (rich in saturated fatty acids) (Brown, Brown, Crowell et al. 1998). Supplementation with menhaden fish oil lowered glomerular capillary pressure, reduced proteinuria, and slowed progressive decline in the glomerular filtration rate (Brown, Brown, Crowell et al. 1998).

Omega-6 fatty acids (which are high in safflower oil) appeared to be detrimental to renal disease (Brown, Brown, Crowell et al. 2000). Brown et al. reported that supplementation with omega-6 polyunsaturated fatty acids (using safflower oil) to dogs with laboratory-induced chronic kidney disease was associated with increased glomerular capillary pressure, glomerular enlargement, and increased eicosanoid excretion rates.

Similar studies have not been reported in cats. Lipid metabolism is complex in cats as they lack the enzyme delta 6 desaturase, suggesting that providing EPA and DHA may be particularly important in this species. One retrospective study of 175 cats with chronic kidney disease suggested that survival time was longer for cats fed diets with high concentrations of EPA (Plantinga et al. 2005). It is clear that further research is needed to evaluate the efficacy of long-chain omega-3 fatty acid supplementation in dogs and cats with chronic kidney disease.

Fiber

Fiber is a simple term for a complex family of plant components that cannot be digested by the digestive tract of

the dog or cat. Fiber can be broadly classified as soluble, insoluble, fermentable, nonfermentable, or mucilage. Fiber can have multiple beneficial effects on gastrointestinal health and function from supporting the microfloral population to regulating gastrointestinal motility. Alterations in gastrointestinal motility (alterations in duodenojejunal motility and decreased colonic transit time) have been reported in a study of dogs with laboratory induced renal disease (Lefebvre et al. 2001). Constipation can occur in cats with chronic kidney disease. The causes are numerous and include dehydration, reduced gastrointestinal motility, and as a side effect of therapeutic agents, including phosphate binders and calcium channel blockers. Therefore, dietary fiber may have a beneficial role to help promote gastrointestinal health in patients with chronic kidney disease.

Fermentable fiber promotes colonic bacterial multiplication; however, a source of ammonia nitrogen is required for bacterial growth. Nitrogen sources include dietary protein that escapes small intestinal digestion, endogenous proteins (pancreatic, intestinal secretions), sloughed intestinal mucosal cells, and blood urea that diffuses across the intestines with water movement. It has been hypothesized that supplementing the diet with fermentable fiber as a source of carbohydrate nutrition for gastrointestinal bacteria will result in the subsequent utilization of blood urea as a source of nitrogen for growth. Therefore, fecal nitrogen excretion in the form of the bacterial cell mass will be increased, urinary nitrogen excretion will be decreased, and the need for protein restriction alleviated. Studies in partially nephrectomized rats have documented a decrease in blood urea concentration; however, there was no net change in total nitrogen excretion, just a shift from urinary to fecal excretion (Younes, Garleb et al. 1998; Younes, Remsey et al. 1997). There have not been any studies published to date to validate this hypothesis in dogs or cats. Furthermore, the clinical relevance of a reduction in blood urea concentration is unknown as urea is a nitrogen marker and not considered a uremic toxin. The traditional uremic toxins are classified as middle molecules and hence too large to move freely with water across the intestinal barrier. Clearly more research is needed in this area before widespread recommendations can be made.

Antioxidants

Oxidation is the loss of an electron from a chemical species. Removal or loss of an electron from a chemical compound produces a free radical. Free radicals are highly reactive as they search for an electron from surrounding molecules to stabilize their structure. Free radicals are able to attack numerous compounds in the body, including lipids, proteins, and nucleic acids. Oxidative damage to these core biological components has been hypothesized to be involved in the etiology or the progression of a number of diseases or conditions including cancer, atherosclerosis, arthritis, aging, cardiovascular disease, and diabetes mellitus. Free radical damage has also been implicated as a contributing factor in the progression of chronic kidney disease in humans (Cochrane and Ricardo 2003; Locatelli et al. 2003).

Humans with chronic kidney disease have been shown to have oxidative stress by evidence of lower concentrations of vitamin E and vitamin C, and high concentrations of markers of lipid peroxidation (Cochrane and Ricardo 2003; Locatelli et al. 2003). It has been hypothesized that cats and dogs with chronic kidney disease may also have oxidative stress (Brown 2008).

The body contains a number of compounds and systems designed to protect against oxidative stress. This protective system includes enzymes such as superoxide dismutase and GSH reductase, peptides such as glutathione, and some vitamins, such as tocopherols, vitamin A and associated retinoids, and vitamin C. Various minerals are also required for the activity of many antioxidant enzymes. Nutritional interventions in which exogenous antioxidants such as vitamin E, vitamin C, taurine, carotenoids, and flavanols are added to the diet are also an effective way to promote a more favorable redox status in the body so that less oxidative damage can occur (Brown 2008). Together, the antioxidant systems collectively function to scavenge and neutralize free radicals and minimize oxidative stress.

Studies in rats and humans have suggested that vitamin E supplementation may slow the progression of chronic kidney disease by modulating tubulointerstitial injury, proteinuria, and glomerulosclerosis (Tahzib et al. 1999; Hahn, Krieg et al. 1999; Hahn, Kuemmerle et al. 1998; Tain et al. 2007). Yu and Paetau-Robinson (2006) reported that supplementation with vitamin E, β-carotene, and vitamin C in cats with naturally occurring stage II chronic kidney disease reduced markers of DNA damage. Brown (2008) reported that supplementation with vitamin E, carotenoids, and lutein to dogs with surgically induced renal mass reduction slowed the rate of reduction of the glomerular filtration rate, compared to dogs that did not receive antioxidant supplementation. Therefore, it is clear that dietary antioxidants can be beneficial to dogs and cats with chronic kidney disease. What remains to be determined by further studies is the actual dose and synergistic combination of dietary antioxidants that is most effective.

Nutrients That Target the Endothelium

Endothelial cells have a key role in maintaining vascular homeostasis by the generation of nitric oxide produced by the endothelial enzyme nitric oxide synthetase. Nitric oxide has a critical role in renal hemodynamics and urine production by dilating both the afferent and efferent arteriole, augmenting glomerular filtration rate and influencing the renal handling of sodium along the tubule segments. Accordingly, endothelial dysfunction is characterized by alterations in vasodilation and vasoconstriction, increased oxidative stress and inflammation, deregulation of thrombosis and fibrinolysis, and abnormal smooth muscle cell proliferation. Endothelial dysfunction is thought to contribute to systemic hypertension, glomerular pathology, progressive proteinuria, and tubular interstitial inflammation and fibrosis in human and animal models of disease. Endothelial dysfunction arises by decreased bioavailability of nitric oxide at the vascular level. There are several proposed mechanisms of action by which endothelial cell dysfunction arises in renal disease. These include a reduction in the renal synthesis of L-arginine, the precursor of nitric oxide; oxidative stress, which reduces nitric oxide release from the endothelium and stimulates the production of profibrotic mediators from the endothelium; and the accumulation of asymmetric dimethylarginine (ADMA), an inhibitor of endothelial nitric oxide synthase. Increasing attention is currently focused on ADMA, which is an endogenous amino acid that is structurally similar to L-arginine. ADMA competes with L-arginine as a substrate for endogenous nitric oxide synthetase. Jepson et al. (2007) reported that ADMA accumulates in cats with naturally occurring stages II, III, and IV chronic kidney disease, and the plasma concentration of ADMA correlated with the creatinine concentration.

There have not been any studies to date to evaluate the effect of nutrients on endothelial cell dysfunction in cats or dogs with chronic kidney disease. However, there are several approaches that can be considered, including supplementation with flavanols, antioxidants such as vitamin E, vitamin C, taurine, lutein, lycopene, or β-carotene and L-arginine. Flavanols, a subclass of flavonoids, are polyphenolic antioxidants that are found in a variety of plants. Flavanols increase the endothelial production of nitric oxide. They are effective antioxidants that trap free radicals generated by circulatory disorders within the glomeruli that occur in chronic kidney disease and have an antihypertensive action. L-arginine may increase the production of nitric oxide and counteract the inhibition induced by ADMA. However, the effect of L-arginine supplementation on human and rodent models of chronic kidney disease is controversial, and further studies are clearly warranted before widespread supplementation can be recommended (Cherla and Jaimes 2004).

Clinical Efficacy

Several studies have been published evaluating the effect of dietary therapy in patients with naturally occurring chronic kidney disease (Elliott, Rawlings et al. 2000; Jacob et al. 2002; Leibetseder and Neufeld 1991; Ross, Osborne et al. 2006). To date, these studies have used "renal" diets that included a combination of nutrient alterations compared to maintenance diets. Therefore, it is not possible to speculate which of the nutrient alterations is responsible for differences in outcome between groups. Nevertheless, the evidence from these clinical studies indicates that nutritional intervention is clearly warranted for pets with naturally occurring chronic kidney disease.

The effect of a modified-protein, low-phosphate diet on the outcome of 50 cats with stable, naturally occurring stage II/III chronic kidney disease has been reported by Elliott and colleagues (Elliott, Rawlings, Markwell et al. 2000). Twenty-nine of 50 cats received a modified-protein, low-phosphate diet, and the remaining 21 of 50 cats remained on their normal diets. The median survival time of the cats fed the modified-protein, low-phosphate diet was significantly greater than the cats fed their normal maintenance diet (633 days vs. 264 days, $P < 0.0036$). The results of this study suggest that feeding a renal diet to cats with chronic renal failure will double their life expectancy.

Ross and colleagues, using a randomized controlled masked clinical trial, evaluated the effect of a renal diet on time to uremic crisis or renal death in 45 cats with naturally occurring stage II/III chronic kidney disease (Ross, Osborne et al. 2006). The renal diet was associated with a significantly lower number of uremic crises and renal related deaths compared to a maintenance diet.

Leibetsder and Neufeld (1991) evaluated the effects of feeding diets with a low phosphorus and moderately restricted protein content in dogs with mild to moderate chronic kidney disease. Thirty-two dogs were fed a low-phosphorus, medium-protein commercial diet for 28 weeks, and an additional 28 dogs were fed a homemade diet formulated to mimic the commercial diet. Within 4 weeks of feeding either the commercial or the homemade diet, the concentrations of blood urea nitrogen and phosphorus had almost normalized.

Jacob and colleagues evaluated the effect of a modified-protein, low-phosphate diet on the outcome of 28 dogs with stable, naturally occurring stage III chronic kidney disease (Jacob, Polzin, Osborne et al. 2002). Dogs that

were fed a renal diet had a 70% reduction in the relative risk of developing a uremic crisis, remained free of uremic signs almost two and a half times longer, and had a median survival that was three times longer than dogs with chronic kidney disease that were fed a maintenance diet.

Administration

The efficacy of nutritional therapy depends on the diet being fed consistently and exclusively. Humans afflicted with kidney disease, and presumably cats and dogs with chronic kidney disease, have altered senses of taste and smell. Cats in particular also have a strong likelihood of developing food aversion, which arises when adverse events such as hospitalization and blood sampling are associated with feeding. In this regard, it is advisable not to institute dietary changes when patients are hospitalized. Rather, the renal support diet should be instituted in the home environment. In addition, the diet must be palatable enough to avoid any risk of refusal. Practical measures to improve food intake include the use of highly odorous foods, warming the foods prior to feeding, and stimulating eating by positive reinforcement with petting and stroking behavior. Appetite stimulants may be judiciously administered; however, in cases where adequate daily energy intake cannot be achieved, more aggressive therapy employing enteral feeding tubes is clinically indicated (Elliott, Riel et al. 2000). Feeding tubes (see Chapter 20) should be instituted for nutritional support upon documentation of a 10–15% loss of body weight in conjunction with a declining body condition score and a history of poor dietary intake. Feeding tubes are also advantageous as they circumvent the need for subcutaneous fluid therapy (since water intake can be controlled by the caretaker) and ease the administration of oral medications.

Concurrent Diseases

Chronic kidney disease is a common condition of the dog and cat, and although it can occur in younger animals, it is typically a disease of the middle-aged to older pet. It is not unusual for the older pet to have two or more chronic disease conditions. In some situations, the nutritional management of these diseases appears diametrically opposed, for example, the management of the dog with chronic kidney disease and a history of recurrent pancreatitis or hyperlipidemia; a cat with diabetes mellitus and chronic kidney disease; a patient with a diagnosis of adverse food reaction and chronic kidney disease, etc. Clearly for many of these disease combinations, the ideal commercial therapeutic diet may not initially appear to be available. In some situations, a commercial solution can be found by careful analysis of the true needs of the patient coupled with a detailed review of the nutritional features of the commercially available diets. A plethora of commercial diets specifically designed for renal disease are available, and these diets do differ in both ingredients and concentrations of nutrients. Furthermore, some diets specifically designed for mature or senior pets may have controlled levels of phosphate and/or fat concentrations that are adequate to control the serum phosphate concentrations for pets with early stage disease or chronic pancreatitis. The nutrient levels of the various diets must be compared on an energy basis, that is, per 1,000 kcal or Mcal. Comparison on an as-fed or dry matter basis does not elucidate true nutritional differences due to variations in the water and energy contents of the diets.

With respect to adverse food reactions, the most important point is to carefully review the history and diagnosis to clearly ascertain that a true food allergy exists, versus a perceived food allergy or an adverse reaction to food. In some cases, the owner is convinced that a food allergy exists on the basis of a response to unsupervised dietary changes or serum allergy testing, neither of which are reliable criteria for an absolute diagnosis of food allergy. Evaluation of the diet that is currently being fed may indeed reveal that the patient is already eating the purported allergenic ingredients and yet does not have any clinical signs.

Cases will always remain for which a commercial diet cannot be identified to meet the nutritional needs of the patient. In these situations, a compromise can be made to select a commercial diet that meets the needs of the most life-threatening disease. Alternatively, a home-prepared diet can be formulated for the pet.

Home-prepared diets are neither convenient nor economical for the client. Unlike commercially available foods, home-prepared diets have not been adequately tested with animal feeding trials or laboratory analysis to confirm nutrient content and nutrient availability. Home-prepared diets are often crudely balanced and may not achieve satisfactory palatability, digestibility, or safety. Furthermore, owners are likely to substitute different ingredients without understanding the full ramifications. Ingredient substitution or deletion, especially elimination of the vitamin and mineral supplements, is likely to unbalance the diet. Ingredient substitution and elimination can arise because of the inconvenience in obtaining the ingredients, the expense of the ingredients, or from a failure to understand the importance of strictly adhering to the recipe.

Home-prepared diets can provide adequate nutrition and assist in the management of disease processes provided

that a properly formulated diet is used, the correct ingredients are included, and the recipe is strictly adhered to. Formulating a home-prepared diet requires a complete understanding of the nutrient requirements of the pet and the effect of the disease process on the nutritional requirements. Detailed nutrient analyses of the ingredients selected and a thorough knowledge of dietary interactions are needed. Finally, knowledge of the effect that preparation and storage has on nutrient availability is necessary.

Homemade diet recipes can be obtained from the veterinary literature, textbooks, and the Internet (see Chapter 8). However, caution should be applied when retrieving recipes from the Internet or lay publications. These recipes should be scrutinized to ensure that they are indeed complete and balanced for the pet or that they have the appropriate nutritional modifications to indeed help assist the management of a disease process. Consulting with a board-certified veterinary nutritionist is the best option to obtain a diet specifically designed for the pet requiring a home-prepared diet.

Monitoring

Chronic kidney disease is a dynamic condition that can have multiple and variable effects on all body systems. No two patients are alike in presentation, complications, or response to therapy. Therefore, regular monitoring is crucial to ensure that dietary and medical management remains optimal for the needs of the patient. Owner compliance may also be improved by frequent patient evaluation. Patients should be reevaluated within 2 weeks of initiating therapy and then at minimum, three to four times per year. Reevaluations should always be made 2 weeks following medication or dietary change. Certain medical therapies such as erythropoietin and antihypertensive therapy will initially require weekly evaluation until the appropriate maintenance dosage is achieved.

A complete history including diet history, physical examination, body weight, body condition score, and laboratory evaluation including complete blood count, biochemical panel, urine analysis, urine protein to creatinine ratio, urine culture, and blood pressure evaluation is typically indicated. Urine culture should be a routine procedure in follow-up examinations, as patients with chronic kidney disease are predisposed to urinary tract infections. These patients are typically asymptomatic, or clinically "silent," and yet chronic urinary tract infections may progress to pyelonephritis, acute or chronic kidney disease, or contribute to progression of the kidney disease.

A complete list of all medications and doses that the client is currently administering to the pet should be obtained to verify compliance. In addition, some owners will self-adjust medications or simply may be confused by previous instructions. The diet history should include the type of diet (dry vs. wet), the amount eaten each day (amount eaten is more important than amount offered), the method of feeding, and information regarding all treats, snacks, and supplements should also be obtained to be able to assess if dietary management and caloric intake are appropriate.

ACUTE RENAL DISEASE

Protein calorie malnutrition has been implicated as a possible factor influencing outcome in human patients with acute renal failure (ARF) (Leonard et al. 1975). Although there have been no reported studies evaluating the effect of nutritional status on the duration, outcome, or recovery of renal function in canine and feline ARF patients, protein calorie malnutrition appears to be common and is a major factor contributing to morbidity and mortality. Factors contributing to malnutrition include inadequate intake of nutrients as dietary intake is compromised by uremic-induced consequences of anorexia, nausea and vomiting,

Summary of Key Nutritional Factors

	Stage I	Stage II	Stage III	Stage IV
Hydration	Fresh water at all times			
Protein modification	Dogs: UPC > 2 Cats: UPC > 0.4	Dogs: UPC > 0.5 Cats: UPC > 0.4	Appropriate dietary protein reduction to control uremia and hyperphosphatemia	
Control phosphate		2.7 to 4.5 mg/dl	<5 mg/dl	<6 mg/dl
Control acidosis	Maintain bicarbonate 18–24 mmol/l			
Control potassium	Control at all stages within species-specific reference intervals			
Prevent protein calorie malnutrition	Feeding tube intervention when not eating RER or 10–15% loss of body weight			

and coexisting catabolic illnesses. In addition, recovery from ARF may require prolonged convalescence during which animals are hypercatabolic, azotemic, hyperkalemic, acidotic, and hyperphosphatemic. Malnutrition and wasting may contribute to many aspects of the uremic syndrome, including impaired immune function, increased susceptibility to infection, delayed wound healing, decreased strength and vigor, and poor quality of life. Therefore, early nutritional assessment and institution of nutritional support is crucial in the management of patients with ARF. Furthermore, nutritional supplementation should be individually tailored to compensate for the specific abnormalities in protein, carbohydrate, and lipid metabolism, and the marked alterations in fluid, electrolyte, and acid base balance characteristic of ARF. Oliguria and anuria are complications that significantly influence the nutritional management of the patient with acute renal failure.

Metabolic status among patients with ARF varies; however, most patients have some degree of protein catabolism and negative nitrogen balance (Mitch 1998). Patients are more likely to be catabolic when the acute renal failure is caused or associated with shock, sepsis, or rhabdomyolysis (Feinstein et al. 1981). Catabolism and marked protein breakdown in turn contribute to uremic syndrome by exacerbating hyperkalemia, hyperphosphatemia, acidosis, and azotemia.

The optimum nutritional regime for controlling accelerated catabolism and the precise nutritional requirements for dogs and cats with ARF are unknown, but a high-energy, moderate-protein, potassium- and phosphate-restricted diet comparable to those for chronic kidney disease are logical choices. ARF is a dynamic disease; hence serial clinical and laboratory assessment of the patient and modification of dietary therapy in response to changes in the patient's condition is integral to successful therapy.

Sufficient energy needs to be provided to prevent endogenous protein catabolism, which results in malnutrition and exacerbation of azotemia. Oxygen consumption has shown to be reduced in rats with experimental ARF; however, humans with ARF have an increased oxygen consumption (Schneeweiss et al. 1990). This may be due to the presence of coexisting complications including sepsis and multiple organ failure. Therefore, energy metabolism in ARF varies and depends on the presence of underlying disease. It is generally considered that there is a decrease rather than an increase in energy expenditure. The energy expenditure of an individual patient may be assessed by indirect calorimetry; however, this technique is not widely available in veterinary hospitals. The energy intake of the patient can be calculated as the resting energy requirement (RER) of $70(Wt_{kg})^{0.75}$. Excessive energy intake should be avoided particularly in animals with compromised respiratory function as the increased carbohydrate and fat metabolism generates CO_2.

The dietary protein requirements for cats and dogs with acute renal failure are not known and may be influenced by the extent of protein catabolism and coexistent illnesses. Peritoneal dialysis and hemodialysis may also increase protein requirements to compensate for substrate loss during therapy (Elliott, Marks et al. 2000). Ideally, protein intake should be matched with catabolism to promote a positive nitrogen balance. However, measurement of total nitrogen output to determine nitrogen balance is too laborious and expensive to be widely applied for clinical use.

Phosphorus and potassium intake should be restricted to prevent accumulation of these minerals; however, intakes must be modified according to the clinical status of the patient (see the section on potassium). Patients with ARF are often anorexic, have reduced appetites and often severe gastrointestinal ulceration secondary to uremia. In addition, an altered sense of taste and smell has been reported in people (Atkin-Thor et al. 1978). These factors in combination contribute to reduced caloric intake and refusal of diet. Effective dietary management can be facilitated by the placement and use of enteral feeding devices (see Chapter 20). Enteral feeding can be achieved by the administration of blended commercial prescription diets or formulated liquid diets. The feeding solution can be administered intermittently or continuously using a syringe pump. Typically, feeding begins with one-quarter to one-third of the calculated daily RER. The amount and concentration of the solution should be gradually increased over several days until the nutritional requirements are met. Several enteral formulations have been specifically developed for use in renal disease in humans; however, these products may contain inadequate amounts of protein and amino acids such as taurine and arginine, and hence should be used cautiously in dogs and cats. Concentrated protein supplements may be utilized to supplement enteral products to the desired protein concentration.

Peripheral parenteral nutrition (PPN) or central parenteral nutrition (CPN) is indicated if the nutrient requirements cannot be met by the enteral route and the patient can tolerate the additional fluid load. This additional fluid load is often the limiting factor in the nutritional management of the oliguric or anuric ARF patient. PPN involves the administration of isotonic nutritional solutions through

a peripheral vein, thereby avoiding the requirement of a central vein necessary for the administration of hyperosmolar parenteral nutrition solution. PPN cannot typically provide the complete nutritional requirements for a patient because the solution is required to be isotonic in order to avoid thrombophlebitis. A PPN solution is typically formulated with a combination of 5% dextrose solution, 8.5% amino acid solution, and 20% lipid solution to provide approximately 50% of the RER, and an osmolality of 300 to 400 mOsm/L. Therefore, PPN should only be used as an adjunct to supplement oral intake or to supply partial temporary nutritional support in animals that are expected to return to a normal oral intake in less than 5 days.

CPN refers to the provision of most of the essential nutrients and because of the hyperosmolality of the solution, requires administration into a central vein such as the cranial vena cava. CPN is indicated to allow time for vomiting to cease and gastrointestinal recovery to occur, at which time a commercial renal failure diet can be substituted enterally. Parenteral nutrition is expensive. It requires aseptic formulation and administration in addition to specialized monitoring procedures to avoid sepsis and metabolic complications (Armstrong and Lippert 1988). Modified amino acid formulations for human patients with ARF are available. These preparations are more expensive than the standard amino acid formulations and have been formulated on the hypothesis that endogenous urea could be utilize to synthesize nonessential amino acids. However, several human studies suggest that the standard amino acid solutions are as effective as modified amino acid solutions in ARF.

It is difficult to overcome the catabolic state in uremia and achieve positive nitrogen balance with nutritional support alone. Therefore, recent interest has focused on evaluating pharmacological strategies to promote anabolism in patients with ARF. Metabolic interventions including the administration of insulin, anabolic steroids, growth hormone, thyroid hormone, antiglucocorticoids, insulin-like growth factor-1, β-2 adrenergic agonists, intracellular proteolytic pathway inhibitors, adenine nucleotides, glutamine, arginine, ribonucleic acid, or omega-3-fatty acids to facilitate the anabolic process, reduce protein degradation, or enhance the immune system are currently being evaluated as nutritional adjunctives in human medicine. The efficacy of these interventions in patients with ARF remains to be seen.

GLOMERULAR DISEASE

The term "glomerular disease" represents a diverse array of disorders of different pathogenic mechanisms, morphological expressions, clinical courses, and response to therapy in which the glomerulus is the sole or principal tissue involved. The hallmark and indeed one of the earliest functional defects in glomerular disease is the loss of plasma protein in the urine (proteinuria) with inactive urinary sediment. The consequences of proteinuria include sodium retention, edema and/or ascites, hypercholesterolemia, hypertension, hypercoagulability, muscle wasting, and weight loss.

The management of glomerular disease encompasses reversing or eliminating the underlying antigenic stimulation in order to halt progression of the disease, and partnering dietary therapy with appropriate pharmacological management (Lees et al. 2005). In most cases, specific antigens or antigenic sources cannot be identified. Indeed, in a study of 106 dogs with glomerular disease an underlying cause could not be found in 43% of cases (Cook and Cowgill 1996).

The appropriate diet for glomerular disease appears to be a moderately protein-restricted, controlled-sodium, and long-chain omega-3 fatty-acid-enhanced diet. This may seem counterintuitive as the seemingly logical approach to protein-losing disease may be to increase the protein intake of the patient. However, Burkholder et al. (2004) reported that the magnitude of proteinuria increased when dogs with X-linked hereditary nephropathy were placed on a higher protein (36.4% DMB) versus a lower protein diet (14.1% DMB). Studies in rats suggest that high-protein diets are actually detrimental to glomerular disease as the additional protein load increases glomerular capillary pressure, exacerbates proteinuria, and increases progression of renal disease. Restricting the dietary protein intake of nephrotic subjects actually reduces proteinuria and increases total body albumin mass and serum albumin concentrations.

Humans with protein-losing nephropathies have been reported to have additional nutritional deficiencies, primarily associated with the loss of protein-bound vitamins and minerals. However, studies of nutrient deficiencies associated with protein-losing nephropathies have not been reported in dogs or cats. It would seem rational that minimizing proteinuria, maintaining lean body mass, and ensuring appropriate daily caloric intake of a complete and balanced diet would help to minimize vitamin and mineral deficiencies.

There have been limited studies on the efficacy of dietary modification in glomerular disease. Valli et al. (1991) reported that a renal therapeutic diet could delay the onset and decrease the severity of renal disease in dogs with X-linked hereditary nephritis. There have been no

studies that the author is aware of in cats, although there is renewed interested in the importance of proteinuria in chronic kidney disease (see the section on protein above).

FANCONI SYNDROME

Fanconi Syndrome is a disease that affects the proximal renal tubule, resulting in defective transport of water, glucose, phosphate, sodium, potassium, amino acids, and bicarbonate (Yearley et al. 2004). The disease has been reported to be inherited in Basenjis and Norwegian Elkhounds, with sporadic occurrences in other breeds and cats. Fanconi Syndrome can also be an acquired disease secondary to drugs such as gentamicin therapy and toxins like heavy metals. A recent outbreak of Fanconi-like disease has also been reported in Australia in association with the consumption of chicken-jerky treats (Thompson et al. 2009).

Bicarbonaturia, amino aciduria, glycosuria, phosphaturia, and uricosuria can have several metabolic consequences including hyponatremia, hypokalemia, hyperchloremic metabolic acidosis, hypophosphatemia, and hypocalcemia. Most dogs do not have renal disease at the time of diagnosis; however, the development of acute renal disease due to severe metabolic acidosis and papillary necrosis is a realistic clinical concern. Indeed, renal failure has been reported to be the most common reason for death or euthanasia of affected dogs (Yearley et al. 2004).

Management needs to be customized to the individual patient and revolves primarily around management of the clinical and metabolic signs: polyuria, azotemia, acidosis, and hypokalemia. Hypokalemia is common and is due to the resorptive defect of bicarbonate: Bicarbonaturia enhances renal potassium excretion. Treatment should be targeted at both the impairment in bicarbonate reabsorption by providing sodium bicarbonate therapy and by providing oral potassium supplementation to manage the hypokalemia.

Hydration should be ensured by providing adequate fresh water at all times. For dogs with no evidence of renal disease, the most appropriate diet would be a good quality, highly digestible diet for adult dogs. The "Gonto Protocol" has been designed by Basenji enthusiasts and enjoys widespread anecdotal success (Gonto 2003). However, studies have not been reported that compare the efficacy of this therapy to alternative approaches. Once the patient has evidence of renal disease, dietary alterations as discussed above for chronic kidney disease would be appropriate; however, protein intake should be carefully monitored to ensure maintenance of lean body mass and to minimize the adverse consequence of protein deficiency.

CONCLUSION

Diet plays an important role in the management of patients with kidney disease. Nutritional therapy introduced in stages II and III of chronic kidney disease is aimed at factors that delay progression, whereas, once late stage III/IV disease has been reached, clinical signs of uremia are evident, and dietary treatment is designed more to improve the quality of life of the patient than to slow disease progression. Regular monitoring to ensure that dietary and medical management remains optimal for the needs of the patient is crucial for the long-term successful treatment of the patient with kidney disease. Regardless of the disease, the diet must be tailored to the individual needs of the patient, and adjustments are to be expected throughout the course of treatment. Clinical studies have clearly proven that nutrition can improve the life expectancy and significantly minimize the risk of uremic crises in patients with chronic kidney disease.

SUMMARY

- Dietary therapy in kidney disease is only effective if it is administered appropriately.
- Kidney disease is dynamic, hence the nutritional requirements need to be tailored to the individual and altered according to the metabolic status of the patient.
- Nutritional alterations in stage II and III disease are focused on slowing the progression of kidney disease.
- Management of stage IV disease is designed to alleviate the clinical manifestations of the uremic syndrome.
- Studies have clearly shown that feeding a renal diet to pets with kidney disease will ameliorate the clinical signs and slow disease progression.

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Nutritional Management of Lower Urinary Tract Disease 16

Joe Bartges and Claudia Kirk

INTRODUCTION

Lower urinary tract disease occurs commonly in cats and dogs. Previous estimates of the incidence in cats in the United States and United Kingdom were 0.85 to 1.0% per year (Willeberg 1984; Lawler, Sjolin et al. 1985), while in dogs the incidence is 2.0 to 3.0% per year (Thomsen, Svane et al. 1986). These estimates are based on presence of clinical signs only and did not consider actual diagnoses. Any disorder of the lower urinary tract may cause signs of lower urinary tract disease. In cats younger than approximately 10 years of age, idiopathic cystitis and urolithiasis occur most commonly (Kruger, Osborne et al. 1991; Buffington, Chew et al. 1997), while in cats older than 10 years of age, bacterial urinary tract infection and urolithiasis occur most commonly (Bartges 1996). In dogs, the incidence of lower urinary tract disease increases with advancing age; bacterial urinary tract infections and urolithiasis occur most commonly (Bartges 2000; Lulich, Osborne et al. 2000).

CRYSTAL-RELATED LOWER URINARY TRACT DISEASE

Of the various causes of lower urinary tract disease, crystal-related disease accounts for 15–45% of cases. There are many minerals that may precipitate in the urinary tract to form crystals and stones; however, more than 90% of uroliths from cats and dogs are composed of either struvite (magnesium ammonium phosphate hexahydrate) or calcium oxalate monohydrate or dihydrate. Struvite is the most common mineral observed to occur in matrix-crystalline urethral plugs.

Urolith and matrix-crystalline plug formation involves complex physiochemical processes. Major factors include: (1) urine supersaturation resulting in crystal formation (nucleation); (2) effect of inhibitors of mineral nucleation, crystal aggregation, and crystal growth; (3) crystalloid complexors; (4) effects of promoters of crystal aggregation and growth; (5) effects of noncrystalline matrix; and (6) and urine retention or slowed transit for the process to occur (Brown and Purich 1992; Coe, Parks et al. 1992). Urethral matrix-crystalline plugs have only been identified in male cats and may represent an intermediate phase between lower urinary tract inflammation without crystals and urolith formation (Osborne, Lulich et al. 1996). The most important driving force behind urolith formation is urinary supersaturation with calculogenic substances (Bartges, Osborne et al. 1999a); however, as mentioned before, other factors are important. The goal of urinary crystal-related disease is to promote a reduced state of urinary saturation.

Urolithiasis

Urolithiasis refers to the formation of and consequences of mineral precipitation within the urinary system. It is not a single disease with a single cause, but the sequelae of multiple underlying abnormalities. Therefore, it can be viewed as a syndrome defined as the combination of pathophysiological factors (familial, congenital, and/or

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acquired) that increase risk of precipitation of minerals in the urinary system forming uroliths.

Calcium Oxalate

Figures 16.1, 16.2, and 16.3 show a calcium oxalate dehydrate urocystolith in a dog.

Calcium oxalate uroliths form when urine is oversaturated with calcium and oxalate (Bartges, Osborne et al. 1999a). In addition to these alterations in activities of ions, large molecular weight proteins that occur in urine, such as nephrocalcin, uropontin, and Tamm-Horsfall mucoprotein, influence calcium oxalate formation (Balaji and Menon 1997). We have a limited understanding of the role of these macromolecular and ionic inhibitors of calcium oxalate formation in cats and dogs. Certain metabolic factors are known to increase the risk of calcium oxalate urolith formation in several species. Medical and nutritional strategies for stone prevention have focused on amelioration of these factors.

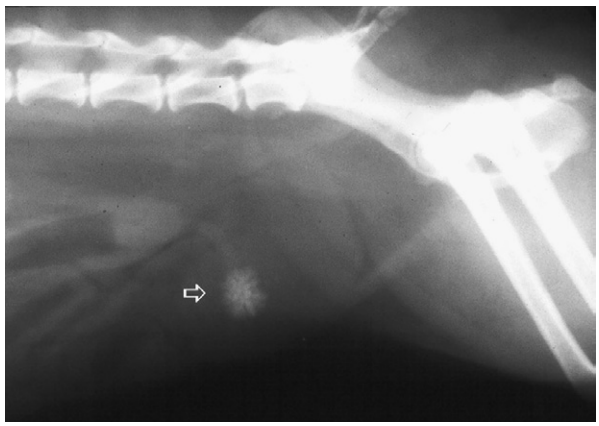

Fig. 16.1. Lateral abdominal radiograph of an 8-year-old, castrated male Miniature Schnauzer with a urocystolith composed of calcium oxalate dihydrate (arrow).

Hypercalcemia is associated with increased risk of calcium oxalate urolith formation. In cats with calcium oxalate uroliths, hypercalcemia was observed in 35% of the cases (Bartges 2001). Conversely, uroliths developed in 35% of cats with idiopathic hypercalcemia (Midkiff, Chew et al. 2000). In dogs with calcium oxalate uroliths, hypercalcemia has been observed to occur in approximately 5%; usually these dogs have primary hyperparathyroidism (Lulich, Osborne, Thumchai et al. 1999). Hypercalcemia results in increased calcium fractional excretion and hypercalciuria when severe.

Hypercalciuria is a significant risk factor, but not necessarily the cause of calcium oxalate urolith formation in human beings, dogs, and cats (Bartges, Kirk, and Lane 2004). Hypercalciuria can result from excessive intestinal absorption of calcium (GI hyperabsorption), impaired renal reabsorption of calcium (renal leak), and/or excessive skeletal mobilization of calcium (resorptive) (Coe, Parks et al. 1992). In Miniature Schnauzers, GI hyperab-

Fig. 16.2. Calcium oxalate dihydrate urocystolith removed from dog in Fig. 16.1.

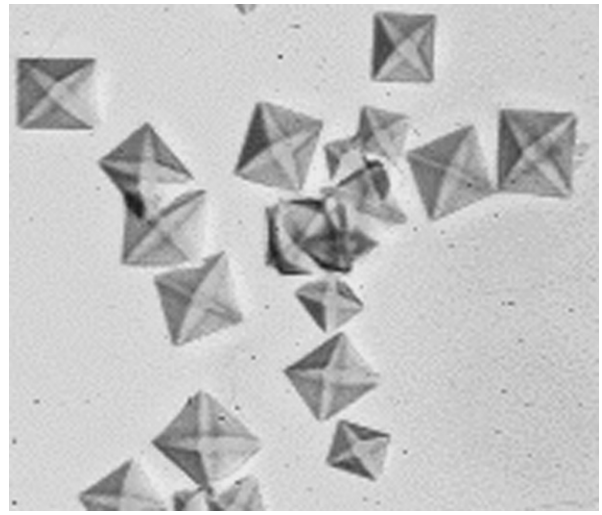

Fig. 16.3. Calcium oxalate dihydrate crystals from dog in Fig. 16.1.

sorption appears to occur most commonly, although renal leak hypercalciuria has also been observed (Lulich, Osborne et al. 1991). Hypercalciuria has not been well defined in normocalcemic cats with calcium oxalate uroliths but is thought to occur.

Hyperadrenocorticism is associated with increased risk of calcium oxalate urolith formation in dogs (Hess, Kass et al. 1998). The mechanisms for the increased risk are unknown; however, we have observed hypercalciuria and increased urinary saturation for calcium oxalate in dogs with hyperadrenocorticism and calcium oxalate uroliths (Kraje, Bartges et al. 2000). The degree of hypercalciuria was decreased with medical management of hyperadrenocorticism.

Metabolic acidosis promotes hypercalciuria by promoting bone turnover (release of calcium with buffers from bone), increasing serum ionized calcium concentration resulting in increased urinary calcium excretion, and decreased renal tubular reabsorption of calcium. Consumption of diets supplemented with the urinary acidifier ammonium chloride by cats has been associated with increased urinary calcium excretion (Ching, Fettman et al. 1989). Aciduria (urine pH < 6.2) may represent a risk factor for calcium oxalate formation because of acidemia and hypercalciuria. In addition, acidic urine alters the function and concentration of crystal inhibitors. Low urine pH decreases urinary citrate concentration by increasing renal proximal tubular citrate reabsorption. Acidic urine is known to impair function of macromolecular protein inhibitors. In a study of healthy cats, urinary saturation for calcium oxalate was less at a urine pH of 7.2 compared with 6.8 or 6.2 when the only variable was the acidification or alkalinization potential of the diet (Bartges, Kirk et al. 2004).

Inhibitors, such as citrate, magnesium, and pyrophosphate, form soluble salts with calcium or oxalic acid and reduce availability of calcium or oxalic acid for precipitation. Other inhibitors, such as Tamm-Horsfall glycoprotein and nephrocalcin, interfere with the ability of calcium and oxalic acid to combine minimizing crystal formation, aggregation, and growth.

Oxalic acid is a metabolic end product of ascorbic acid (vitamin C) and several amino acids, such as glycine and serine, derived from dietary sources. Oxalic acid forms soluble salts with sodium and potassium ions, but a relatively insoluble salt with calcium ions. Therefore, any increased urinary concentration of oxalic acid may promote calcium oxalate formation. Dietary increases of oxalate and vitamin B6 deficiency are known factors increasing urinary oxalate. Hyperoxaluria has been observed experimentally in kittens consuming vitamin B6-deficient diets, but has not been associated with naturally occurring calcium oxalate urolith formation. Genetic anomalies may also increase urine oxalic acid concentration. Hyperoxaluria has also been recognized in a group of related cats with reduced quantities of hepatic D-glycerate dehydrogenase, an enzyme involved in metabolism of oxalic acid precursors (primary hyperoxaluria type II) (McKerrell, Blakemore et al. 1989). Hyperoxaluria has also been associated with defective peroxisomal alanine/glyoxylate aminotransferase activity (primary hyperoxaluria type I) and intestinal disease in human beings (enteric hyperoxaluria). These have not been evaluated in cats or dogs.

Decreased urine volume results in increased calcium and oxalic acid saturation and an increased risk for urolith formation. Cats can achieve urine specific gravities in excess of 1.065, indicating a marked ability to produce concentrated urine. Many cats and dogs affected with calcium oxalate uroliths have a urine specific gravity > 1.040 unless there is some impairment of renal function or concentrating ability (Bartges, Kirk, and Lane et al. 2004).

The detection of calcium oxalate crystals indicates that urine is supersaturated with calcium oxalate, and, if persistent, this supersaturation represents an increased risk for calcium oxalate urolith formation. However, calcium oxalate crystalluria is present in fewer than 50% of feline and canine cases at time of diagnosis of urolithiasis (Bartges, Kirk, and Lane 2004).

Medical protocols that will promote dissolution of calcium oxalate uroliths are not currently available; therefore, uroliths must be removed physically: either surgically, by cystoscopy and laser lithotripsy, or by voiding urohydropropulsion (Lulich, Osborne, Sanderson et al. 1999; Adams, Berent et al. 2008; Lulich, Osborne et al. 2009).

Nutritional and/or medical protocols should be considered to minimize urolith recurrence or prevent further growth of uroliths that remain in the urinary tract. A significant number of cats and dogs will develop recurrent uroliths within 2 years of their initial episode if prevention protocols are not initiated (Lulich, Osborne et al. 2004). If possible, metabolic factors known to increase calcium oxalate risk should be corrected or minimized. The goals of dietary prevention include: (1) reducing urine calcium and oxalate concentration, (2) promoting high concentrations and activity of urolith inhibitors, (3) reducing urine acidity, and (4) promoting dilute urine.

Increasing urine volume is a mainstay of preventative therapy for calcium oxalate urolithiasis in human beings. By increasing water intake, urinary concentrations of

calculogenic minerals are reduced. In addition, larger urine volumes typically increase urine transit time and voiding frequency, thereby reducing retention time for crystal formation and growth. Feeding a canned food is the most practical means of increasing water intake and lowering calcium oxalate urine saturation. The goal is to dilute urine to a specific gravity of ≤ 1.030 (Kirk, Ling et al. 2003). Flavoring water, enhancing water access, and adding water to dry foods may be used in pets that refuse to eat canned foods.

Consumption of high levels of sodium may augment renal calcium excretion in human beings. Epidemiological evidence suggests that the low dietary sodium levels in cat and dog foods increase the risk for calcium oxalate urolithiasis and diets that contain high dietary sodium levels decrease the risk (Lekcharoensuk, Osborne et al. 2001; Lekcharoensuk, Lulich, Osborne et al. 2000a, 2000b). Recent studies in healthy cats and dogs did not find increased urine calcium excretion in response to high dietary salt intake (minimal 1.2% sodium dry matter basis) (Kirk, Ling et al. 2003; Stevenson, Hynds et al. 2003; Lulich, Osborne et al. 2005). In humans with hypocitraturia, sodium supplementation increased urine volume and decreased urinary saturation for calcium oxalate (Stoller, Chi et al. 2009). In one study, when fed a food lower in sodium, cats with naturally occurring calcium oxalate uroliths excreted less urine calcium (Lulich, Osborne et al. 2004). In healthy cats or those with marginal renal function and hypercalciuria, increased dietary sodium exacerbated calcium excretion with (Kirk, Jewell et al. 2006) and without (Hughes, Slater et al. 2002; Buranakarl, Mathur et al. 2004; Luckschander, Iben et al. 2004; Cowgill, Sevgev et al. 2007; Xu, Laflamme et al. 2009) increasing azotemia. Furthermore, in another study, restricting dietary sodium was associated with kaliuresis, an increased risk of hypokalemia, and a decrease in glomerular filtration rate in cats with induced chronic renal failure (Buranakarl, Mathur et al. 2004). Until further data are available, orally administered sodium chloride or use of loop diuretics, which promote renal sodium excretion, for diuresis should be used cautiously and with careful monitoring as it may increase the risk of calcium oxalate urolith formation or worsening azotemia in some patients. Recommended levels of sodium in foods for cats and dogs predisposed to calcium oxalate formation is unknown as diets containing as low as 0.4 g/1,000 kcal sodium and as high as 3.5 g/1,000 kcal sodium are available commercially.

The solubility of calcium oxalate in urine is influenced by pH and epidemiologic studies consistently identify acidifying diets among the most prominent risk factors for calcium oxalate urolithiasis (Kirk, Ling et al. 1995; Thumchai, Lulich et al. 1996; Lekcharoensuk, Lulich et al. 2000a, 2000b). In prospective studies, however, the influence of pH directly on calcium oxalate solubility is less clear with one study showing no influence (Stevenson 2002) and another showing an increase in calcium oxalate solubility at a pH of 7.2 (Bartges, Kirk et al. 2004). In a case series of five cats with idiopathic hypercalcemia and calcium oxalate uroliths, discontinuation of acidifying diets or urinary acidifiers was associated with normalization of serum calcium concentration (McClain, Barsanti et al. 1999). In another study of healthy cats, urinary saturation for calcium oxalate linearly decreased with increasing urine pH (Bartges, Kirk et al. 2004). Although conclusions from one study were that urinary pH and potassium citrate had limited effects on urinary saturation for calcium oxalate in dogs, three Miniature Schnauzers, a breed with a higher risk for calcium oxalate formation, had lower urinary saturation for calcium oxalate with potassium citrate supplementation and alkaluria (Stevenson, Wrigglesworth et al. 2000). Aciduria promotes hypocitraturia and functional impairment of endogenous urolith inhibitors. Thus, feeding an acidifying diet or administering urinary acidifiers to cats and dogs at risk for calcium oxalate is contraindicated. A target urine pH of approximately 7.5 is suggested in cats and dogs at risk for the recurrence of calcium oxalate uroliths (Kirk, Ling et al. 2003; Bartges, Kirk et al. 2004) despite conflicting evidence (Stevenson 2002).

Although reduction of urine calcium and oxalic acid concentrations by restriction of dietary calcium and oxalic acid appears logical, it is not without risk. Reducing consumption of only one of these constituents may increase availability and intestinal absorption of the other, resulting in increased urinary excretion. Conversely, increasing dietary calcium levels contributes directly to increased urine calcium concentration. Because epidemiologic data suggest marked dietary calcium restriction increases urolith risk, moderate levels of dietary calcium are advised in nonhypercalcemic cats (Lekcharoensuk, Lulich et al. 2000a; Lekcharoensuk, Osborne et al. 2002; Lekcharoensuk, Osborne et al. 2002; Kirk, Ling et al. 2003).

Urinary oxalate is derived from endogenous metabolism of oxalate precursors (i.e., glycine and ascorbic acid) and dietary oxalic acid. Most pet food ingredients are low in oxalic acid, with the exception of vegetables, legumes, and several vegetable-based fermentable fibers (e.g., beet pulp and soybean fiber). Dietary oxalic acid concentrations should be reduced to the lowest possible level. Suggested

levels are < 20 mg oxalic acid/100g of food (dry matter basis).

Excess intake of vitamin C, a metabolic oxalate precursor, should similarly be avoided (Kirk, Ling et al. 2003). While normal dietary vitamin C levels are not considered a risk in human beings, very small increases in urinary oxalate are a concern in urolith formers. Because cats and dogs do not have a dietary vitamin C requirement, supplementation should be avoided. Cranberry concentrate tablets are also contraindicated. They provide mild acidification and are high in oxalate, as well as vitamin C (Terris, Issa et al. 2001); however, in one study of human beings, cranberry juice ingestion resulted in increased citrate and decreased oxalic acid in urine (McHarg, Rodgers et al. 2003).

Potassium citrate is often included in diets designed for calcium oxalate prevention. In urine, citric acid combines with calcium to form soluble complexes, thereby reducing ionic calcium concentration and directly inhibiting nucleation of calcium and oxalate crystals (Tiselius, Berg et al. 1993; Caudarella and Vescini 2009). Administration has also been associated with decreased urinary oxalate excretion (Ito 1991), decreased intestinal calcium absorption resulting in decreased urinary calcium excretion (Rumenapf and Schwille 1987), and increased excretion and activity of urinary inhibitory macromolecules (Caudarella and Vescini 2009). When oxidized within the tricarboxylic acid cycle, supplemental citrate results in urine alkalinization due, in part, to production of bicarbonate (Rodman 1991; Hamm and Simon 1987) although short-term administration of citrate does not have this effect (Sakhaee, Alpern et al. 1992). The metabolic alkalinization increases endogenous renal citrate excretion and reduces calcium absorption and urinary excretion (Pak, Fuller et al. 1985; Kirk, Ling et al. 2003). Commercial products that add citrate but continue to acidify the urine (pH < 6.5) reduce the benefit of citrate therapy.

Dietary phosphorus should not be restricted with calcium oxalate urolithiasis. Low dietary phosphorus is a risk factor for calcium oxalate urolith formation in cats and dogs (Lekcharoensuk, Lulich et al. 2000; Lekcharoensuk, Osborne et al. 2001; Lekcharoensuk, Osborne et al. 2002; Lekcharoensuk, Osborne et al. 2002). Reduction in dietary phosphorus may be associated with activation of vitamin D, which in turn promotes intestinal calcium absorption and hypercalciuria. Additionally, phosphate status determines pyrophosphate urinary concentrations, an inhibitor of calcium oxalate urolith formation in human beings and rodents. If calcium oxalate urolithiasis is associated with hypophosphatemia and normal calcium concentration, oral phosphorus supplementation may be considered. Caution should be used, however, because excessive dietary phosphorus may predispose to formation of calcium phosphate uroliths. Whether this occurs in cats is unknown. Phosphorus levels in the foods for cats predisposed to calcium oxalate formation should not be excessive. Diets formulated for oxalate prevention in dogs and cats contain phosphorous from 0.3 to 2.1 g/1,000 kcal. Levels from approximately 1.5 to 2.0 g/1,000 kcal have been recommended (Kirk, Ling et al. 2003).

Urinary magnesium forms complexes with oxalic acid, reducing the amount of oxalic acid available to form calcium oxalate. Studies in cats associate low dietary magnesium with calcium oxalate risk (Robertson 1993; Thumchai, Lulich et al. 1996; Smith, Moodie et al. 1997; Lulich, Osborne, Thumchai et al. 1999; Lekcharoensuk, Lulich et al. 2000; Lekcharoensuk, Osborne et al. 2001). In human beings, supplemental magnesium has been used to minimize recurrence of calcium oxalate uroliths; however, supplemental magnesium may increase the risk of struvite formation in cats. At this time, the risks and benefits of magnesium supplementation to cats and dogs with calcium oxalate urolithiasis have not been evaluated, and supplementation is not advised. It appears logical that magnesium should not be highly restricted in diets that are consumed by cats with calcium oxalate urolithiasis. Many diets that claim to benefit feline "urinary tract health" are reduced in magnesium and promote urinary acidification. These foods are designed for struvite prevention and are not appropriate for cats at risk for calcium oxalate urolithiasis. Prudent levels of dietary magnesium are from 0.08–0.10% dry matter or approximately 200 mg magnesium/1,000 kcal (Lekcharoensuk, Osborne et al. 2001; Kirk, Ling et al. 2003).

Consumption of high amounts of animal protein by human beings is associated with an increased risk of calcium oxalate formation. Dietary protein of animal origin may increase urinary calcium and oxalic acid excretion, decrease urinary citrate excretion, and promote bone mobilization in order to buffer the acid intake from the metabolism of animal proteins. However, a case-controlled, retrospective study showed that higher protein concentration in cat and dog foods appeared protective against calcium oxalate uroliths (Lekcharoensuk, Lulich et al. 2000; Lekcharoensuk, Osborne et al. 2001; Lekcharoensuk, Osborne et al. 2002; Lekcharoensuk, Osborne et al. 2002). Protein levels between 80 and 90 g protein/1,000 kcal appeared most protective in cats. While several coassociations (e.g., higher protein in canned foods) might explain this finding, cats are obligatory carnivores, and dietary

protein restriction in the management of calcium oxalate urolithiasis is not advised.

Excessive levels of vitamin D (which promotes intestinal absorption of calcium) and vitamin C (which is a precursor of oxalic acid) should be avoided. Diets with vitamin D between 250 and 350 IU/1,000 kcal should suffice. As discussed above, vitamin C is an oxalate precursor, as well as a weak urinary acidifier. Both features may increase likelihood of urolith recurrence.

The diet should be adequately fortified with vitamin B6 because vitamin B6 deficiency promotes endogenous production and subsequent urinary excretion of oxalic acid (Bai, Sampson et al. 1989). There is no evidence that increased vitamin B6 beyond that needed to meet the nutritional requirements in cats provides a benefit. Because most commercial diets designed for cats and dogs are well fortified with vitamin B6, it is unlikely additional supplementation will be beneficial except in deficient homemade diets. Regardless, vitamin B6 is reasonably safe and sometimes provided to cats with persistent calcium oxalate crystalluria or frequent recurrences.

Increased dietary fiber intake is associated with decreasing risk of calcium oxalate recurrence in some human beings. Certain types of fiber (soy or rice bran) decrease calcium absorption from the gastrointestinal tract, which may decrease urinary calcium excretion. Also, higher fiber diets tend to be less acidifying. In five cats with idiopathic hypercalcemia and calcium oxalate uroliths, feeding a high-fiber diet with supplemental potassium citrate resulted in normalization of serum calcium concentrations (McClain, Barsanti et al. 1999). In dogs with dietary fat intolerance and calcium oxalate uroliths, consumption of diets containing 8–15% fiber with supplemental potassium citrate appears beneficial anecdotally; however, efficacy of increased fiber intake is unproved at this time.

While the relationship of obesity to urolith formation is not understood, it remains a consistent risk factor in all studies to date. Restricting food intake to obtain an ideal weight and body condition is encouraged.

Cats and dogs that are meal fed on average have a more alkaline urinary pH, controlled food intake for obesity prevention and a lower risk of calcium oxalate urolith formation (Kirk, Ling et al. 1995; Lekcharoensuk, Lulich et al. 2000). This method of feeding is also the preferred choice for canned foods. This is a relatively simple step that owners can take to improve preventative measures.

Although there are several commercially available therapeutic diets for managing calcium oxalate uroliths in cats and dogs, none have been through clinical trials with the end point of urolith recurrence, although there are some data in healthy animals and in pets that have formed calcium oxalate uroliths (Smith, Stevenson et al. 1998; Stevenson, Markwell et al. 2002; Lulich, Osborne et al. 2004). Calcium oxalate uroliths are recurrent with an approximate 36% recurrence within 1 year if preventative measures are not undertaken (Lulich, Perrine et al. 1992). Recommendations for monitoring dogs and cats that have formed calcium oxalate uroliths include complete urinalysis and abdominal radiography every 4 to 6 months. Maintaining a urine pH > 7.0 and urine specific gravity < 1.025 is ideal. In cats with hypercalcemia-associated calcium oxalate urolithiasis, maintain normocalcemia.

Struvite

Figures 16.4, 16.5, and 16.6 show a struvite urolith in a dog.

Struvite is another name for crystals or uroliths composed of magnesium ammonium phosphate hexahydrate. The chemical composition of struvite is $Mg^{2+}NH_4^{+}PO_4^{3-}{*}6H_20$. In order for uroliths to form, urine must be oversaturated with respect to the minerals that precipitate to form that type of urolith. In order for struvite uroliths to form, urine must be oversaturated with magnesium, ammonium, and phosphate ions. Urinary oversaturation with struvite may occur as a consequence of a urinary tract infection with a urease-producing microbe (infection-induced struvite) or without the presence of a urinary tract infection (sterile struvite) (Osborne, Lulich et al. 1990; Bartges, Osborne, Polzin et al. 1992).

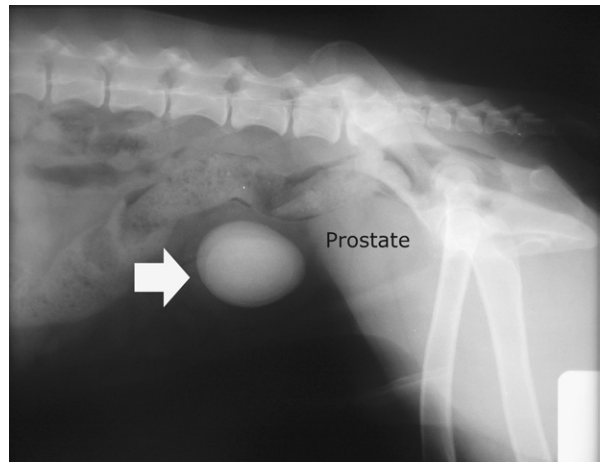

Fig. 16.4. Lateral abdominal radiograph of a 10-year-old mixed breed intact male dog with an infection-induced struvite urocystolith (arrow) and prostatomegaly.

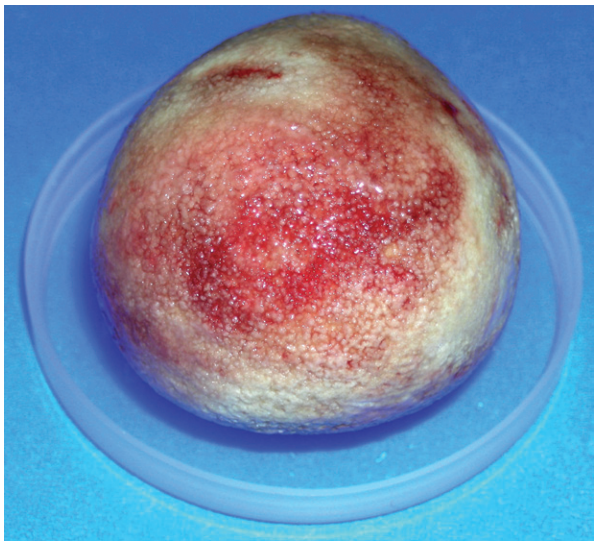

Fig. 16.5. Infection-induced struvite urocystoliths removed from dog in Fig. 16.4.

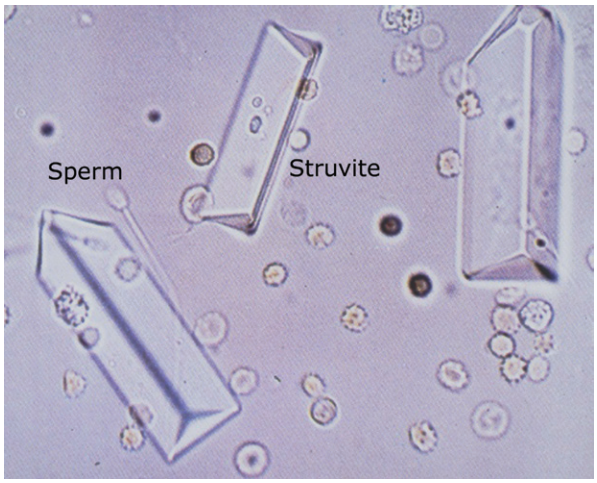

Fig. 16.6. Struvite crystals, sperm, and blood cells from dog in Fig. 16.4.

Sterile Struvite

Sterile struvite uroliths form typically in cats between 1 and 10 years of age, although it has been reported in related English cocker spaniels (Bartges, Osborne et al. 1992). Risk for struvite urolith formation decreases after approximately 6–8 years of age in cats (Smith, Moodie et al. 1997). They occur with equal frequency in male and female cats. Sterile struvite uroliths form because of dietary composition as well as innate risks for urolith formation. Experimentally, magnesium phosphate and struvite uroliths formed in healthy cats that consumed calculogenic diets containing 0.15 to 1.0% magnesium (dry matter basis) (Finco, Barsanti et al. 1985; Osborne, Polzin et al. 1985; Buffington 1989). These data are difficult to interpret; however, because the amount of magnesium consumption by cats in these studies may be different than the amount consumed by cats that spontaneously form sterile struvite uroliths because of the differences in commercial diets with regard to caloric density, palatability, and digestibility (Osborne, Kruger et al. 1999). The influence of magnesium on struvite formation depends on urine pH (Buffington, Rogers et al. 1990) and the influence of ions, minerals, and other components in urine (Buffington, Blaisdell et al. 1994). Alkaluria is associated with increased risk for struvite formation (Tarttelin 1987a; Bartges, Tarver et al. 1998). In a clinical study including 20 cats with naturally occurring struvite urocystoliths and no detectable bacterial urinary tract infection, the mean urinary pH at the time of diagnosis was 6.9 ± 0.4 (Osborne, Lulich et al. 1990). An additional factor is water intake and urine volume. Consumption of increased quantities of water may result in lower concentrations of calculogenic substances in urine, thus decreasing the risk of urolith formation (Smith, Stevenson et al. 1998). Frequent consumption of small quantities of food rather than one or two large meals per day is associated with production of more acidic urine and a lesser degree of struvite crystalluria in cats (Tarttelin 1987b; Finke and Litzenberger 1992).

Sterile struvite uroliths can be dissolved by feeding a diet that is magnesium-, phosphorous-, and protein-restricted, and that induces aciduria relative to maintenance adult cat foods (Osborne, Lulich et al. 1990). In a clinical study including 22 cats with sterile struvite urocystoliths, urocystoliths dissolved in 20 cats in a mean of 36.2 ± 26.6 days (range, 14–141 days) (Osborne, Lulich et al. 1990). The cats were fed a high-moisture (canned), calorically dense diet containing 0.058% magnesium (dry matter basis) and increased sodium chloride (0.79% dry matter basis). The diet induced a urine pH of approximately 6.0. Sterile struvite uroliths dissolve on average in 2 to 4 weeks (Osborne, Lulich et al. 1990). A urinalysis and lateral abdominal survey radiograph should be performed every 4 weeks until urolith dissolution. The diet should be continued for 2 weeks past radiographic evidence of dissolution. If uroliths do not dissolve, uroliths may contain other minerals or not be composed of struvite,

and surgery or a minimally invasive technique should be performed to remove them.

Prevention of sterile struvite uroliths involves inducing a urine pH less than approximately 6.8, increasing urine volume, and decreasing the excretion of magnesium, ammonium, and phosphorous. There are many diets available that are formulated to be "struvite preventative," although none have published information concerning recurrence rates. The goals for prevention of sterile struvite urolithiasis include maintaining a urine pH of 6.0–6.5 and a lack of struvite crystalluria. Whether inducing dilute urine is beneficial is unknown; however, a target urine specific gravity of < 1.040 may be realistic.

Infection-Induced Struvite

Infection-induced struvite uroliths occur more commonly in dogs, but are reported to occur in cats less than 1 year and greater than 10 years of age. They are more likely to occur in female dogs, but no gender predilection has been identified in cats. Infection-induced struvite uroliths form because of an infection with a urease-producing microbe in a fashion similar to human beings (Osborne, Polzin et al. 1985). In this situation, dietary composition is not important, as the production of the enzyme, urease, by the microbial organism is the driving force behind struvite urolith formation.

Infection-induced struvite uroliths can be dissolved by feeding a "struvite dissolution" diet and administering an appropriate antimicrobial agent based on bacteriological culture and sensitivity. Average dissolution time for infection-induced struvite uroliths is approximately 70 days (Osborne, Lulich et al. 1990; Osborne 1999). It is important that the patient receive an appropriate antimicrobial agent during the entire time of medical dissolution because bacteria become trapped in the matrix of the urolith, and as the urolith dissolves, bacteria are released into urine. If therapeutic levels of an appropriate antimicrobial agent are not present in urine, then an infection will recur, and dissolution will cease. A urinalysis and lateral survey abdominal radiograph should be performed every 4 weeks until urolith dissolution. When successful, uroliths decrease in size and number by approximately 50% every 4 weeks until disappearance. The struvite dissolution diet and antimicrobial therapy should be continued for 2 to 4 weeks past radiographic evidence of urolith dissolution. If uroliths do not dissolve, then surgery or a minimally invasive technique should be performed to remove them.

Prevention of infection-induced struvite does not require feeding a special diet as it is the infection that causes these struvite uroliths to form. It involves preventing a bacterial urinary tract infection from recurring and treating bacterial infections as they arise. Dietary manipulation will not prevent infection-induced struvite uroliths from recurring because diet will not prevent recurrence of a bacterial urinary tract infection.

Purines

Uric acid is one of several biodegradation products of purine nucleotide metabolism (Bartges, Osborne et al. 1999b). In most dogs and cats, allantoin is the major metabolic end product; it is the most soluble of the purine metabolic products excreted in urine. Purine accounted for approximately 5–8% of feline and canine uroliths submitted to the Minnesota Urolith Center from 1981 to 2002; most are composed of urate salts with < 0.2% composed of xanthine. Ammonium urate is the monobasic ammonium salt of uric acid, and it is the most common form of naturally occurring purine uroliths observed to occur in dogs and cats (Osborne, Bartges et al. 2000). Other naturally occurring purine uroliths include sodium urate, sodium calcium urate, potassium urate, uric acid dihydrate, and xanthine.

Urate

Figures 16.7, 16.8, and 16.9 show urate uroliths in a Dalmatian, and Figs. 16.10, 16.11, and 16.12 show urate uroliths in a Pomeranian with a portosystemic shunt. Figure 16.13 shows xanthine crystals in a cat.

Urate uroliths occur when urinary concentration of uric acid, and usually ammonium ion, is increased. This may occur secondary to portovascular anomalies (particularly in young animals) (Bartges, Cornelius et al. 1999), but may occur in certain breeds of dogs (e.g., Dalmatians and English bulldogs) (Bartges, Osborne, Lulich et al. 1994) or cats (e.g., domestic shorthair); in dogs without portovascular anomalies, males appear to be affected more frequently than females, but in cats, as well as in animals with portovascular anomalies, males and females appear to be each as likely to be affected. Most urate uroliths occur before 4 years of age. Urate uroliths that occur in association with portovascular anomalies are most commonly composed of ammonium urate and are often diagnosed before 1 year of age.

There have been, apparently, few studies of the biological behavior of ammonium urate uroliths in dogs with portal vascular anomalies (Marretta, Pask et al. 1981; Hardy and Klausner 1983; Johnson, Armstrong et al. 1987; Brain 1988) and none in cats. It is logical to hypothesize that elimination of hyperuricuria and reduction of urine

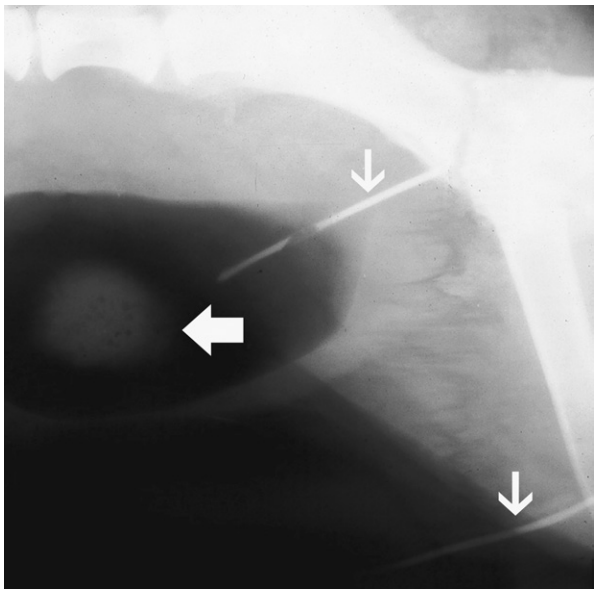

Fig. 16.7. Lateral double contrast cystogram of a 4-year-old castrated male Dalmatian with ammonium urate urocystoliths. The urocystoliths collect in the dependent portion of the contrast (large arrow). Small arrows point to an 8-French red rubber urinary catheter containing contrast inserted transurethrally.

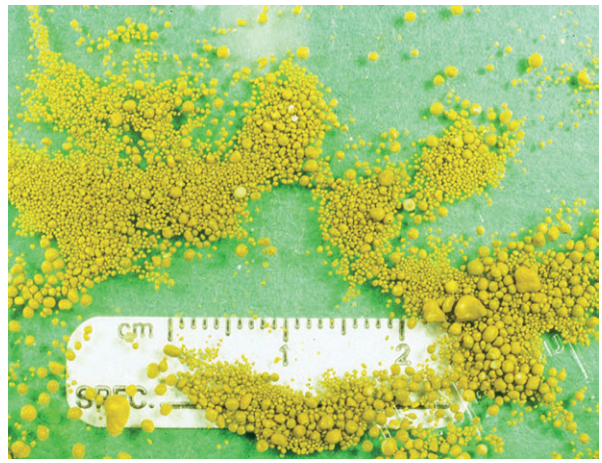

Fig. 16.8. Ammonium urate urocystoliths removed from dog in Fig. 16.7.

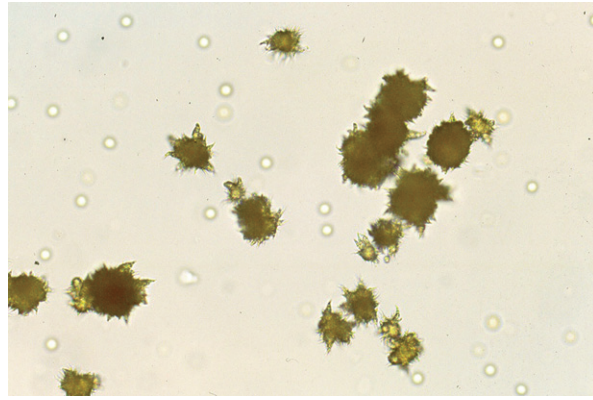

Fig. 16.9. Ammonium urate crystals from the dog in Fig. 16.7.

ammonium concentration following surgical correction of anomalous shunts would result in spontaneous dissolution of uroliths composed primarily of ammonium urate. Appropriate clinical studies are needed to prove or disprove this hypothesis. The authors have occasionally been successful in medically dissolving urate uroliths in dogs with portal vascular anomalies by decreasing dietary purine intake and administering a low dose of allopurinol (5–10 mg/kg PO q 12 h), but have not attempted dissolution in cats with ammonium urate uroliths and portal vascular anomalies.

Medical dissolution of ammonium urate uroliths in dogs without portovascular anomalies is possible by feeding a diet that is protein and purine restricted (approximately 35–50 g/1,000 kcal) and induces a diuresis and alkaluria, and by administering allopurinol (15 mg/kg PO q 12 h) (Bartges, Osborne et al. 1999b). This combination is effective in approximately one-third of dogs with a reduction of size and number of urate uroliths facilitating nonsurgical removal (voiding urohydropropulsion or catheter-assisted retrieval) in one-third; in the remaining one-third of dogs, uroliths did not change or increased in size and number (associated with xanthine formation) (Bartges, Osborne, Koehler et al. 1994). A urinalysis and either abdominal ultrasonography or a double contrast cystogram should be performed every 4 weeks. Urine pH should be > 7.0, and urate crystals should not be present. Uroliths should decrease in size and number by 50% every 4 weeks until gone. If uroliths do not dissolve, then surgery or a minimally invasive procedure should be performed to remove them.

Allopurinol is a synthetic isomer of hypoxanthine. It rapidly binds to, and inhibits the action of, xanthine oxidase, and thereby decreases production of uric acid by inhibiting the conversion of hypoxanthine to xanthine, and

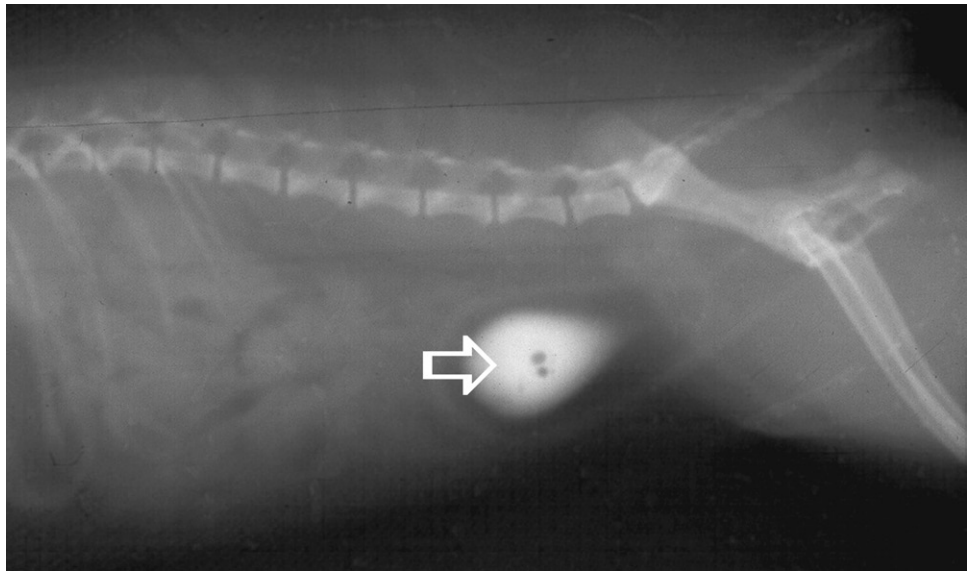

Fig. 16.10. Lateral double contrast cystogram of a 3-year-old castrated male Pomeranian with ammonium urate urocystoliths (arrow).

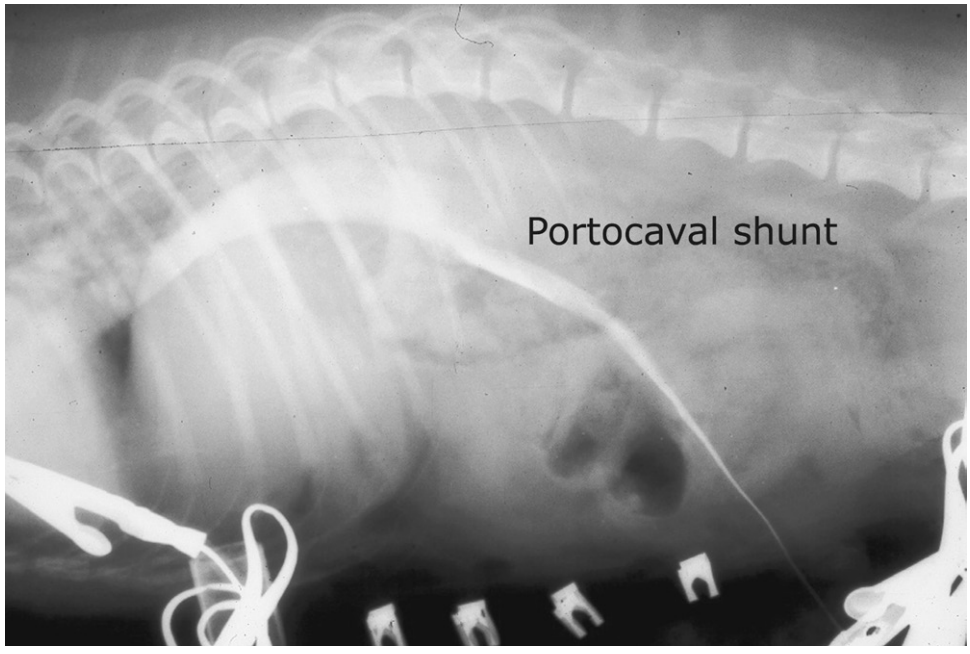

Fig. 16.11. Contrast portal radiography from dog in Fig. 16.10 demonstrating a portocaval vascular shunt.

Fig. 16.12. Ammonium urate urocystoliths removed from dog in Fig. 16.10.

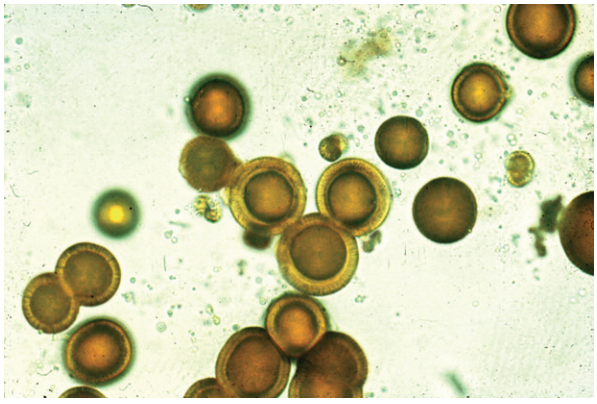

Fig. 16.13. Xanthine crystals from a 3-year-old castrated male domestic shorthair cat.

xanthine to uric acid. The result is a reduction in serum and urine uric acid concentration within approximately 2 days, and a concomitant but lesser degree of increase in the serum concentrations of hypoxanthine and xanthine. The authors have given this dosage to nonazotemic urate-urolith-forming dogs for up to 6 months without detectable consequences; however, when owners supplemented the diet with foods containing purine precursors, a layer of xanthine formed around ammonium urate uroliths or pure xanthine uroliths formed (Bartges, Osborne et al. 1992). Therefore, to minimize xanthine formation, allopurinol should be administered only to animals consuming purine-restricted foods. There is only one report of a possible immune-mediated reaction (hemolytic anemia, trigeminal neuropathy) to allopurinol administration in a dog (Pedroia 1981). The authors observed cutaneous erythema in a Dalmatian given allopurinol and ampicillin. Apparently, this may occur in human beings that are administered this combination of medication. Discontinuation of the ampicillin, but not the allopurinol, resulted in resolution of the skin lesions. Because allopurinol and its metabolites are dependent on the kidneys for elimination from humans, the dosage is commonly reduced in patients with renal dysfunction. Allopurinol has been reported to cause life-threatening erythematous desquamative skin rash, fever, hepatitis, eosinopenia, and further decline in renal function when given to human patients with renal insufficiency. Appropriate precautions should be used when considering use of allopurinol in dogs with primary renal failure.

Although no studies have been performed that evaluate the efficacy or safety of medical dissolution of urate uroliths in cats with idiopathic urate urolithiasis, the authors have successfully dissolved urate uroliths in cats using a low-protein, "renal failure" diet (50–65 g protein/1,000 kcal) and allopurinol (7.5 mg/kg PO q 12 hr). Until further studies are performed to confirm the safety and efficacy of medical dissolution, surgical removal remains the treatment of choice for urate uroliths in cats.

Prevention of urate uroliths in dogs and cats without portovascular anomalies is aimed at reducing urinary concentrations of uric acid and ammonium ions, and inducing diuresis and alkaluria. Feeding diets formulated for "renal failure" in cats or diets that are restricted in purines to dogs are effective in > 90% of cases (J.W. Bartges, personal communication, 2010). Administration of an alkalinizing agent (potassium citrate at 75 mg/kg PO q 12 h) may be required to achieve a urine pH > 7.0. In dogs, administration of allopurinol (7–10 mg/kg PO q 12–24 h) may also be required to prevent urate uroliths from re-forming; prophylactic allopurinol therapy has not been evaluated in cats. Urinalysis and abdominal ultrasonography or double contrast cystography should be performed every 4 to 6 months to monitor effectiveness of prevention. Urine pH should be > 7.0 and urine specific gravity should be < 1.025 (dogs) and 1.035 (cats), and urate crystalluria should not be present.

In dogs and cats with portovascular anomalies, correction of the anomaly often is all that is required to prevent urate uroliths from re-forming. In some animals with congenital liver disease (e.g., microvascular dysplasia), surgical correction is not possible. Preventative therapy in these patients is aimed at decreasing urinary concentrations of uric acid and ammonium ion and at managing signs of hepatoencephalopathy (see Chapter 14).

Xanthine

Xanthine uroliths may form in cats and dogs given allopurinol, especially if dietary protein and purine content is not restricted. Discontinuing allopurinol while restricting dietary protein and purine content may result in dissolution of xanthine in these patients (Bartges, Osborne, Koehler et al. 1994). Allopurinol may be restarted at 25–35% of the previous dosage.

Xanthine uroliths retrieved and analyzed from cats contain pure xanthine, although a few contain small quantities of uric acid. Of 64 cats that formed xanthine uroliths in one report (Osborne, Bartges, Koehler et al. 2004), none of the cats had been treated with the xanthine oxidase inhibitor, allopurinol. Sixty-one xanthine uroliths were obtained from the lower urinary tract while xanthine uroliths from three cats came from the upper urinary tract. Xanthine uroliths occurred in 30 neutered and 8 non-neutered males and 25 neutered females (the gender of one cat was not specified). The mean age of the cats at the time of diagnosis of xanthine uroliths was 2.8 ± 2.3 years (range = 4 months to 10 years). Eight of the 64 cats were less than 1 year old. Urinary uric acid excretion was similar between eight xanthine urolith-forming cats and healthy cats (2.09 ± 0.8 mg/kg/d vs. 1.46 ± 0.56 mg/kg/d); however, urinary xanthine excretion (2.46 ± 1.17 mg/kg/d) and urinary hypoxanthine excretion (0.65 ± 0.17 mg/kg/d) were higher (neither are detectable in urine from healthy cats).

No medical dissolution protocol for feline xanthine uroliths exists. Prevention involves feeding a diet containing approximately 50–65 g/1,000 kcal of protein that induces alkaluria. Without preventative measures, xanthine uroliths often recur within 3 to 12 months following removal. In 10 cats that consumed the protein-restricted alkalinizing diet and were followed for at least 2 years, only one had a recurrence.

Cystine

Figures 16.14, 16.15, and 16.16 show cystine urocystoliths removed from an English bulldog.

Cystine accounts for fewer than 1% of feline and canine uroliths. They occur with equal frequency in male and female cats, but occur more frequently in male dogs. The mean age of diagnosis of cats and dogs with cystine uroliths is 3 to 4 years (Osborne, Kruger et al. 1999; Osborne, Sanderson et al. 1999). Most cats affected with cystine uroliths are domestic shorthair; English bulldogs, Newfoundlands, and Dachshunds are predisposed (Case, Ling et al. 1992; Bartges, Osborne, Lulich et al. 1994).

Cystine uroliths occur when urine is oversaturated with cystine. Cystine is a disulfide-containing amino acid that

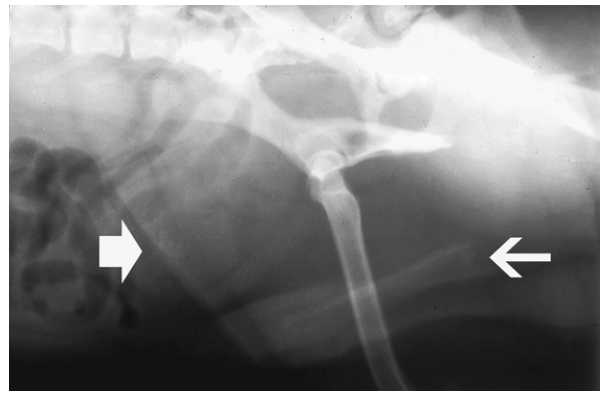

Fig. 16.14. Lateral abdominal radiograph of a 3-year-old intact male English bulldog with cystine urocystoliths (large arrow) and a urethrolith at base of *os penis* (small arrow).

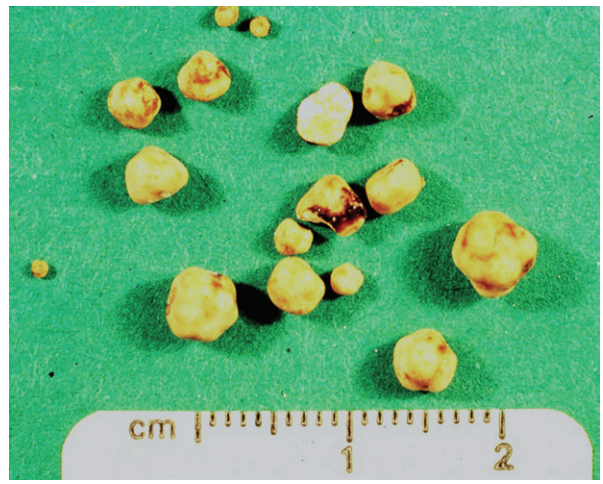

Fig. 16.15. Cystine urocystoliths removed from dog in Fig. 16.14.

is normally filtered and reabsorbed by proximal renal tubular cells. Therefore, cystinuria occurs when there is a defect in proximal renal tubular absorption and must be present for cystine uroliths to form. Evaluation of urine amino acid profiles from cats and dogs with cystine uroliths often reveal increased concentrations of the amino acids cystine, arginine, lysine, and ornithine (Clark and Cuddeford 1971; DiBartola, Chew et al. 1991; Osborne, Kruger et al. 1999).

Medical protocols exist for dissolution of cystine uroliths in dogs utilizing thiol-containing drugs, such as N-(2-mercaptopropionyl)-glycine (2-MPG); the dose for

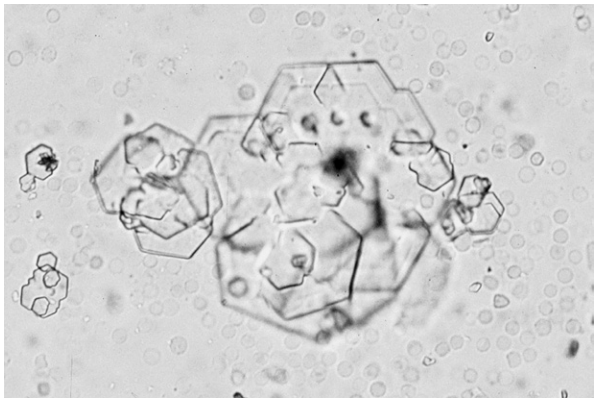

Fig. 16.16. Cystine crystals from dog in Fig. 16.14.

Fig. 16.17. Compound urocystoliths removed from a 10-year-old castrated male toy poodle. The urocystoliths contained a nidus of calcium oxalate and outer layers of struvite, which formed because of a *Staphylococcal* urinary tract infection.

dissolution in dogs is 15 mg/kg PO q 12 h with or without dietary modification (Osborne, Sanderson et al. 1999) or urinary alkalinization. On average, cystine uroliths dissolve in 1 to 2 months; therefore, urinalysis and abdominal radiography should be performed monthly until urolith dissolution (Osborne, Sanderson et al. 1999). Urine pH should be >7.5 and urine specific gravity <1.025. If uroliths do not dissolve, then surgery or a minimally invasive procedure should be performed to remove them.

Prevention of cystine uroliths involves feeding a protein-restricted, alkalinizing diet with or without 2-MPG. Reducing dietary protein has the potential of minimizing formation of cystine uroliths by decreasing intake and excretion of sulfur-containing amino acids and by decreasing renal medullary tonicity, resulting in larger urine volume. The solubility of cystine increases exponentially when the urine pH is greater than 7.2 (Milliner 1990). If necessary, or if dietary modification cannot be done, potassium citrate (initial dose: 75 mg/kg PO q 12 h; titrate to urine pH of 7.5) may be administered to induce alkaluria. For prevention, 2-MPG may be used (Hoppe, Denneberg et al. 1993; Hoppe and Denneberg 2001); however, it is often not necessary with dietary modification (Osborne, Sanderson et al. 1999). Although thiol-containing drugs are used in dogs and human beings, their use has not been evaluated adequately in cats. Urinalysis and abdominal radiography should be performed every 4 to 6 months, and urine pH should be >7.5 and urine specific gravity <1.025 with an absence of cystine crystalluria.

Compound Uroliths

Figure 16.17 shows compound urocystoliths from a Toy Poodle.

Occasionally, uroliths may be composed of more than one mineral. Most commonly, calcium phosphate apatite or ammonium urate may be mixed with struvite when induced by a urease-producing microbial urinary tract infection. These minerals become incorporated into the struvite urolith because ammonium ions produced from the metabolism of urea by microbial urease combine with uric acid, and carbonate produced from metabolism of urea by microbial urease combines with calcium and phosphorous in alkaluria (Osborne, Lulich et al. 1999). Medical dissolution of these uroliths is possible following protocols for dissolution of infection-induced uroliths. Direct preventative measures are toward controlling the causative bacterial urinary tract infection.

Compound uroliths also form when a urolith of one mineral forms and a different mineral precipitates around the first mineral. This occurs most commonly when a calcium oxalate urolith forms and a secondary urinary tract infection with a microbe that produces urease develops, resulting in struvite forming around the calcium oxalate urolith. These uroliths must be removed physically as they cannot be dissolved, and preventative measures are directed toward prevention of calcium oxalate formation.

Surgically and Minimally Invasive Management of Uroliths

Although some uroliths, such as struvite, urate, and cystine, may be dissolved medically, others, such as calcium oxalate and compound uroliths, are not amenable to medical dissolution. Even with uroliths composed of minerals that may be dissolved medically, sometimes it is more desirable to physically remove the uroliths. Physical removal of uroliths may be done by surgery (e.g., cystotomy, urethrotomy, and/or urethrostomy) or by minimally invasive techniques (e.g., catheter-assisted retrieval, voiding urohydropropulsion, cystoscopic removal, and/or cystoscopy with laser lithotripsy) (Lulich and Osborne 1992; Bartges 2000; Adams, Berent et al. 2008; Lulich, Osborne, Albasan et al. 2009; Williams 2009).

Matrix-Crystalline Urethral Plugs

Figure 16.18 shows a matrix-crystalline urethral plug.

Urethral matrix-crystalline plugs occur in approximately 20% of male cats under 10 years of age that present with obstructive lower urinary tract disease (Kruger, Osborne et al. 1991). Urethral plugs have only been observed to occur in male cats. They are composed of at least 45–50% matrix and variable amounts of mineral; they may be composed entirely of matrix (Osborne, Lulich et al. 2003). Struvite is the most common mineral found in urethral plugs. Multiple factors are thought to be associated with urethral plug formation. If a mineral is present in the urethral plug, then risk factors associated with that crystal formation, as discussed previously, are involved, at least in part. Compared with uroliths, urethral plugs contain large quantities of matrix. Components of matrix that may be important in urethral plug formation include Tamm-Horsfall mucoprotein, serum proteins, cellular debris, and virus-like particles (Kruger and Osborne 1990; Osborne, Lulich et al. 1996).

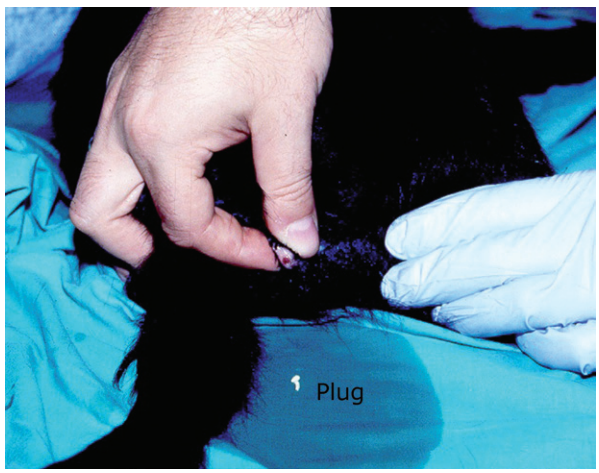

Fig. 16.18. Matrix-crystalline urethral plug expressed from distal urethra of a 6-year-old castrated male domestic shorthair cat with urethral obstruction.

Management of urethral matrix-crystalline plugs involves relieving of the obstructive uropathy (Osborne, Kruger et al. 1996). Modifying urine composition by feeding a therapeutic diet may be beneficial if minerals are present in the urethral plug. Increasing urine volume may help to decrease the concentration of minerals and matrix components in urine. Successful prevention of recurrent urethral obstruction by utilizing diets designed to reduce urine pH and urine magnesium and phosphorous concentrations has been reported (Osborne, Caywood et al. 1991). Perineal urethrostomy may be considered in cats with recurrent urethral plug formation; however, it is associated with complications, including recurrent bacterial urinary tract infections, urethral stricture, and clinical signs of lower urinary tract disease (Osborne, Caywood et al. 1991; Williams 2009). In one study of cats with urethral obstruction due to matrix-crystalline plugs, uroliths, or unidentified causes that were managed medically, recurrence of urethral obstruction occurred in approximately one-third; therefore, surgery may be necessary (Gerber, Eichenberger et al. 2008).

IDIOPATHIC CYSTITIS

The most common cause of lower urinary tract disease in cats less than 10 years of age is idiopathic cystitis (Kruger, Osborne et al. 1991; Buffington, Chew et al. 1997). Idiopathic cystitis is characterized by signs of lower urinary tract disease (i.e., hematuria, stranguria, pollakiuria, and inappropriate urination) without identifiable causes. Often the clinical signs resolve in 3 to 7 days; however, recurrence is variable and unpredictable. Because no specific cause has been identified, no specific treatment is available that works consistently in all cats.

The role of a canned diet in managing cats with idiopathic cystitis has been evaluated in two studies. In one nonrandomized, prospective study of cats with idiopathic cystitis, recurrence of clinical signs occurred in 11% of cats that consumed a canned food when compared with 39% of cats consuming a dry food (Markwell, Buffington et al. 1999). The diets evaluated in this study were acidifying and formulated to prevent struvite crystalluria and urolithiasis. In another study, clinical improvement and

decreased recurrence of clinical signs in cats with idiopathic cystitis were associated with the owners feeding canned foods (Gunn-Moore and Shenoy 2004). The findings of these studies have resulted in the recommendation to feed canned food to cats with idiopathic cystitis; however, these studies were not randomized, controlled trials. Furthermore, specific dietary ingredients have not been evaluated in cats with idiopathic cystitis.

Environmental modification appears to benefit many cats with idiopathic cystitis (Buffington, Westropp et al. 2006). Modifications for indoor cats with idiopathic cystitis include providing a canned diet, good litter box management, climbing structures, an appropriate number of food and water dishes, and increasing water intake.

URINARY TRACT INFECTIONS

Management of urinary tract infections involves eradication or control of predisposing factors and antimicrobial therapy; however, several nutritional strategies may be useful in preventing recurrent bacterial urinary tract infections. Bacterial urinary tract infections occur more frequently in animals with predisposing conditions (e.g., diabetes mellitus, hyperadrenocorticism, chronic renal failure, and hyperthyroidism); therefore, management of these conditions, including diet, may help to decrease recurrent bacterial urinary tract infections (Bartges 2005). Obesity is a common nutritional disorder and the incidence of bacterial urinary tract infections is increased in obese patients.

Bacteria are able to survive in pH from 4 to 9; therefore, feeding an acidifying diet or providing a urinary acidifier is not effective in preventing recurrent bacterial urinary tract infections (Bartges 2005). Cranberry juice or extract has been recommended for preventing recurrent infections. Cranberries contain proanthocyanidins that bind to type 1 and P fimbriae of *Escherichia coli*, thereby preventing adhesion of *Escherichia coli* to the uroepithelium (Howell 2007; Guirguis-Blake 2008; Jepson and Craig 2008; Wing, Rumney et al. 2008; Guay 2009). Despite widespread use and availability, there are few, but some, controlled clinical trials supporting the use of cranberries as prophylaxis. The only *in vitro* study with canine cells did not find benefit (Suksawat, Cox et al. 1996). Probiotics are recommended by some for prevention of recurrent infections. The theory behind probiotics is to modify enteric flora and, ultimately, urogenital flora. There is little evidence of effectiveness; however, certain strains of *Lactobacillus* have been shown to be beneficial in some women and children in controlled studies (Lee, Shim et al. 2007; Reid 2008; Abad and Safdar 2009). There are many botanicals that have been recommended for prevention of urinary tract infections, most commonly *Uva ursi*, which contains tannins and arbutin that may be bactericidal and anti-inflammatory (Head 2008). Little evidence exists for effectiveness. Mannose inhibits adherence of *Escherichia coli* to the uroepithelium *in vitro* by binding to type 1 pilli; however, no clinical studies exist documenting effectiveness *in vivo*.

Not all feline and canine urinary tract disorders are associated with dietary factors; however, most benefit from nutritional management. It is important to understand the pathophysiology of lower urinary tract disease and the physiological effects of foods and feeding in order to formulate the best nutritional and treatment plan.

SUMMARY

- Lower urinary tract disease occurs commonly in dogs and cats with urolithiasis, idiopathic cystitis (cats), and urinary tract infections (dogs) occurring most frequently.
- Uroliths occur when urine is oversaturated with minerals that precipitate. Dietary modification may be useful for medically dissolving and for preventing uroliths. Calcium oxalate and struvite occur most commonly in dogs and cats.
- Dietary modification may also be useful in managing cats with idiopathic cystitis.

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Nutritional Management of Endocrine Diseases

17

Andrea J. Fascetti and Sean J. Delaney

INTRODUCTION

Metabolic regulation occurs on many levels. The diseases discussed in this chapter alter metabolic regulation and energy metabolism. The clinical signs of these diseases are manifested by alterations in subcellular homeostasis. This chapter covers some of the interactions of nutrition with endocrine diseases including diabetes mellitus, lipid disorders, hyperthyroidism, hyperadrenocorticism, and feline idiopathic hypercalcemia, and discusses how nutrition may assist in their management.

DIABETES MELLITUS

Diabetes mellitus is an endocrine disorder that occurs in both cats and dogs. It describes an alteration in cellular transport and metabolism of glucose caused by insufficient insulin release from the pancreas, a lack of insulin receptors, or an inability of the insulin receptors to transduce the signal. This results in elevated glucose levels and an inability of tissues to receive the glucose they need. While there are five primary classifications of diabetes mellitus in humans, applying these classifications to dogs and cats is difficult because familial histories and diagnostic tests used in humans are not readily available (Kirk et al. 1993; Nelson, Feldman et al. 1993). Therefore, the terms insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) are used as they are more clinically relevant. Most dogs with diabetes are classified as IDDM. Cats can be diagnosed with either IDDM or NIDDM. To make things more complicated, cats can have one form and then revert to the other over time. It is hypothesized that beta cell function in these animals can fluctuate, moving them from one category into the next (Zicker et al. 2010).

Dietary management in animals with IDDM does not eliminate the need for insulin replacement, but in some cases it may be used to improve glycemic control. In patients with NIDDM, dietary therapy can also improve glycemic control and may (in some cases) eliminate the need for exogenous insulin therapy. Regardless of the type of diabetes, the following factors should be considered in every patient: overall health and body condition, presence of other diseases, type of diet, nutrient composition of the diet, nutritional adequacy of the diet, the animal's caloric requirement, and feeding schedule.

Nutritional Factors

Water

Often overlooked, water is one of the key nutrients for all animals and is especially important in animals with diabetes. Diabetics have increased water losses associated with an osmotic diuresis secondary to glucose and ketone bodies if diabetic ketoacidosis is present. Fresh and accessible water should be available at all times.

Energy

Many cats and dogs with diabetes have the classic energy-related dichotomy of polyphagia with weight loss. In general, the clinical response of animals with diabetes mellitus to dietary manipulation is dependent upon the level of control of the primary disease process, and presence or absence of secondary diseases. Weight loss may be secondary to poorly controlled diabetes or an

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underlying infection, and weight gain may be due to the presence of another problem such as a thyroid disorder or Cushing's disease.

In cats, like humans, the relationship between obesity and NIDDM is well documented (Rand et al. 2004; Lund et al. 2005; Prahl et al. 2007; Laflamme 2008, 2010). Studies have shown that baseline insulin levels and insulin response to a glucose load increases in dogs as a function of their degree of obesity (Mattheeuws et al. 1984). In cats, the development of feline obesity was accompanied by a 52% decrease in tissue sensitivity to insulin and diminished glucose effectiveness (Appleton et al. 2001). The tissues of other obese species (monkeys and rodents) have decreased numbers of insulin receptors and those receptors that are present have reduced binding affinity. Over time, these changes reduce the body's ability to respond to insulin.

Soluble Carbohydrates

Glucose is one of the most important secretagogues of insulin in healthy subjects. Carbohydrates that are ingested and absorbed result in physiological responses that are dependent upon the rate in which they enter into an animal's system (Jenkins et al. 1981). In humans, a diet that minimizes the glycemic response is desirable because this provides better control of blood glucose and its associated complications. The term "glycemic index" refers to a ranking system for food based on its effects on blood glucose levels. In general, complex carbohydrates (such as barley) have a lower glycemic index than simple carbohydrates (such as potatoes) because they are more slowly digested and absorbed. One study in healthy dogs looked at the glycemic response of five different starch sources: corn, wheat, barley, rice, and sorghum fed at 30% of the diet on a dry matter (DM) basis for 2 weeks (Sunvold and Bouchard 1998). Rice consumption resulted in the highest postprandial glycemic index of the five sources, sorghum the lowest. Wheat and corn generated an intermediate response, and barley had a lower response than wheat and corn. A second study in dogs examined the glucose and insulin response in healthy dogs consuming extruded diets with six different starch sources (cassava flour, brewers rice, corn, sorghum, peas, or lentils) (Carciofi et al. 2008). This study reported greater immediate postprandial and insulin responses (area under the curve < 30 min) for brewers rice, corn, and cassava flour. A similar study examined the same six starch sources in extruded feline diets (de-Oliveira et al. 2008). When compared to the other five starch sources, only corn stimulated an increase in the glucose response at 4 and 10 hours following a meal. Plasma insulin concentrations not only increased when the cats were fed the diet containing corn but also those containing sorghum, peas, and brewers rice.

There has been a trend recently among some veterinarians, animal professionals, and pet owners to malign carbohydrates as an unhealthful food source for dogs and cats. As an obligate carnivore, much of the focus and controversy has centered on the cat. The basis for the argument is that since starch and related carbohydrates were not part of the cat's natural diet, it is unhealthy for such products to be consumed. The simultaneous increase in the use of carbohydrates in many commercial pet foods and the increasing rates of obesity and diabetes mellitus in cats is frequently cited as evidence for this theory. However, the scientific evidence summarized below counters these claims.

Insufficient insulin secretion and impaired insulin sensitivity are the major abnormalities of feline diabetes (Backus 2009). The "carnivore connection" paradigm hypothesizes that these abnormalities are the result of long-term feeding of dietary carbohydrates (Miller and Colaquiri 1994). While it is true that experimentally induced hyperglycemia is detrimental to feline beta-pancreatic cells, the same is true in omnivores (Zini et al. 2009; de-Oliveira et al. 2008). Furthermore, the amount of carbohydrates present in commercial diets has not been shown to induce hyperglycemia (Backus 2009). Three recent population studies further refute the hypothesis that feeding dry-type extruded diets long term are the cause of diabetes in cats (Backus, Cave, and Keisler 2007; McCann et al. 2007; Slingerland et al. 2009).

The association between obesity in cats and the development of diabetes mellitus has been well documented (Rand et al. 2004; Lund et al. 2005; Prahl et al. 2007; Laflamme 2008, 2010). However, epidemiological studies report that obesity is associated with high-fat foods and not high-carbohydrate foods (Scarlett and Donoghue 1998; Lund et al. 2005). In fact, there are some studies that suggest that high-carbohydrate, low-fat diets have an obesity-protective effect (Michel et al. 2005; Backus, Cave, Ganjam et al. 2007). Exchanging dietary carbohydrate for protein does appear to be helpful for weight loss and managing diabetes in some cats (Backus 2009); however, a similar macronutrient exchange does not appear to prevent weight gain in post-ovariohysterectomized cats (Vester et al. 2007; Backus 2009).

Current scientific evidence does not support the argument or negative press that carbohydrates in pet foods are currently receiving. Regardless, such claims continue to circulate so nutritionists will need to continue to educate

veterinarians and the public about the safety and efficacy of carbohydrates, especially when it comes to cat foods.

Fiber

The amount and type of dietary fiber has been the subject of extensive investigation in the management of diabetic patients. For the purposes of this discussion, dietary fiber will be classified into two broad categories: insoluble and soluble fiber. Soluble fibers [e.g., pectins, gums, mucilages, fructooligosaccharides (FOS) and some hemicelluloses] have a high water-holding capacity, delay gastric emptying, slow the rate of nutrient absorption across the intestinal surface, and are highly fermentable by intestinal bacteria. Insoluble fibers (e.g., cellulose, lignin, and most hemicelluloses) have less initial water-holding capacity, decrease gastrointestinal transit time and are less efficiently fermented by gastrointestinal bacteria. Fiber is proposed to promote slowed digestion and absorption of dietary carbohydrate, and reducing insulin peaks after meals. Soluble fibers are also believed to form gels in aqueous solutions, thereby binding glucose and water and preventing their transfer to the absorptive surface of the intestine.

There have been a number of studies examining the use of dietary fiber in diabetic dogs. In one study, dogs with experimentally induced diabetes had significant reductions in 24-hour blood glucose fluctuations when fed a diet containing either 15% (DM) soluble or insoluble fiber (Nelson, Ihle et al. 1991). Dogs consuming the high-fiber diets were consuming fewer calories than the dogs fed the control diet. So this raises the question of whether improved glycemic control was secondary to the fiber, a reduction in calorie intake, or both.

A second study fed dogs with IDDM a canned diet supplemented with either 20 g of wheat bran (insoluble fiber) or 20 g of guar gum (soluble fiber) (Blaxter et al. 1990). Compared to control dogs that consumed the canned diet without added fiber, both fiber sources reduced postprandial hyperglycemia, the wheat bran to a lesser extent than the guar gum. Similar effects were observed in both diabetic and healthy control dogs.

A third study examined the long-term effects of feeding increased amounts of insoluble fiber (cellulose) to dogs with IDDM over two 8-month periods (Nelson, Duesberg et al. 1998). Dogs were either fed 11% or 23% total dietary fiber (DM) in a canned diet. The composition of the diets was similar and caloric intake was controlled to maintain body weight. Nine of the eleven dogs in the study improved with respect to daily insulin requirement, fasting blood glucose, urinary glucose excretion, glycosylated hemoglobin concentrations and serum cholesterol while eating the high-fiber food. The remaining two dogs had better glycemic control when they were eating the low-fiber diet. Overall, when dogs had better glycemic control, they were consuming fewer calories. This finding suggests that caloric intake may have partially influenced glycemic control in this study.

The effects of both insoluble and soluble dietary fiber were examined in a study in dogs with naturally occurring IDDM (Kimmel et al. 2000). Seven dogs were fed one of three dry diets for a 1-month time period. One diet was a low-fiber diet (total dietary fiber not reported), a second diet was a high-fiber diet containing only insoluble fiber (73 g/1,000 kcal ME), and the third diet contained both soluble and insoluble fiber sources (56 g/1,000 kcal ME). The dogs had significantly better glycemic control while consuming the high insoluble fiber diet compared to the other two diets. Fructosamine concentrations were lower in dogs when consuming both fiber-supplemented diets, compared to the low-fiber diet. Although the calorie composition of the diets was similar and caloric intake did not differ between the groups, there were differences with respect to the soluble carbohydrate sources between the diets. It is unknown if this difference had any impact on the findings.

Another study looked at the effect of feeding a high-fiber canned diet containing a blend of insoluble and soluble fibers (Graham et al. 2002). Over the 4-month study, changing to the high-fiber diet was associated with significant reductions in fructosamine concentrations, glycosylated hemoglobin concentrations, cholesterol, and 24-hour glucose concentrations. Body weight declined in the dogs on the study by the fourth month; the authors attributed this to underfeeding the dogs. An increase in dietary fiber consumption or calorie restriction may have been responsible for the positive findings.

There are very few studies evaluating the effects of dietary fiber on naturally occurring diabetes in cats (Nelson, Scott-Moncrieff et al. 2000). Cats in the randomized cross-over study by Nelson et al. were fed a diet containing either insoluble fiber [cellulose, 19% total dietary fiber (DM)] or low insoluble fiber, [4.1% total dietary fiber (DM)] for 24 weeks. Mean preprandial glucose concentrations and 12-hour mean glucose concentrations were significantly lower in the cats eating the high-fiber diet. The carbohydrate content was higher in the low-fiber diet. The authors do not rule out the possibility that the higher starch content in the low-fiber diet may have impacted glycemic control in the participants in this study.

A more recent study looked at the effects of a low-carbohydrate/low-fiber diet compared to a moderate-carbohydrate/high-fiber diet in cats with diabetes mellitus (Bennett et al. 2006). Sixty-eight percent of the cats consuming the low-carbohydrate/low-fiber diet and 41% of the cats eating the moderate-carbohydrate/high-fiber diet were able to discontinue insulin and reverted to a nondiabetic state during the 16-week trial. While these findings suggest that cats are more likely to not need insulin and have their diabetes resolve when consuming a low-carbohydrate/low-fiber diet, perhaps it was not only the amount of carbohydrate and fiber that was responsible for this finding but also the type of digestible carbohydrate. The low-carbohydrate/low-fiber diet contained soybean meal and corn gluten meal whereas the moderate-carbohydrate/high-fiber diet contained ground corn. Corn gluten meal is a high-protein product of corn with most of the soluble carbohydrates extracted and therefore will have a lower glycemic index compared to whole ground corn. Soybean meal has a low glycemic index as well. The use of carbohydrates with a lower glycemic index in the low-carbohydrate/low-fiber diet may have influenced the overall findings of the study.

Research examining the efficacy of fiber supplementation in diabetes has raised a number of questions, perhaps more than it has answered. The above studies support that increasing amounts of insoluble fiber reduce the postprandial glycemic curve. However, is this effect from the fiber or the caloric dilution that occurs secondary to the addition of the fiber? Alternatively, is it related to the amount and type of soluble carbohydrate in the diet? Perhaps it is a combination of both. Furthermore, the ability of fiber to provide long-term health benefits, improve quality of life, or to reduce or eliminate the complications associated with diabetes has not yet been determined.

Fat

Diabetic animals often have accompanying abnormalities in lipid metabolism such as hypertriglyceridemia, hypercholesterolemia, or both. Concurrent pancreatitis is common in many diabetics. Fat should be restricted in patients with these problems. The degree of fat restriction is dependent on the patient's diet history and current fat consumption at the time of diagnosis for both hyperlipidemia (see below) and pancreatitis (see Chapter 13).

Protein

Diabetic animals may have increased amino acid losses through their urine. Patients that are not well controlled will also experience muscle wasting as protein is catabolized to meet energy needs. Currently there are two basic approaches to managing diabetes in dogs and cats, high-carbohydrate/moderate-protein foods or low-carbohydrate/"high-protein" diets (in some cases "high protein" often only translates into the same amount of protein found in typical maintenance diets).

Recent investigations into obesity and the pathogenesis of diabetes mellitus in cats have led to the hypothesis that feline diabetics might have improved glycemic control, or in some cases even revert to a nondiabetic state, when dietary carbohydrate is restricted. One study (only reported as an abstract) in healthy cats demonstrated that lower postprandial glucose concentrations were measured in cats consuming 46% of their calories from protein compared to the same amount provided by fat or carbohydrates (Farrow et al. 2002). Calorie intake was not reported in the cats, and the differences in the composition of the diets were not addressed.

There have been several clinical trials in diabetic cats investigating the potential benefits of feeding low-carbohydrate, protein-replete or high-protein diets. The first study evaluated 18 cats consuming a diet with 33% of the calories provided by protein, 8% of the calories from carbohydrates and a hypoglycemic agent, acarbose (Mazzaferro et al. 2003). Cats were classified as responders (insulin discountinued) and nonresponders (continued to require insulin or glipizide). Eleven of the cats were no longer receiving insulin by the fourth month of the study. Overall, responders lost weight during the study, and nonresponders had significantly less body fat than cats that did respond. Both responders and nonresponders had similar decreases in serum glucose and fructosamine concentrations.

Another clinical trial fed what the authors referred to as a high-protein canned diet in nine cats for 3 months (45% protein and 45% fat calories) (Frank et al. 2001). All of the cats were initially adapted to a high-fiber canned diet (38% protein and 37% fat calories) for a standardization period of 1 month prior to the study. The cats remained stable on the high-protein canned diet, and most owners thought their cats were slightly more active. In three cats, insulin was discontinued, although serum fructosamine concentrations increased in these cats following insulin removal. There was no diet effect on serum glucose concentrations.

It is difficult to discern from the above research which nutrient modifications are having a positive impact. There appears to be some clear evidence that supplementation with insoluble fiber helps to reduce the glycemic response and assists in managing diabetic patients. The results of

carbohydrate restriction or protein augmentation are less clear. With respect to the research in cats, the amount of protein fed in some of the studies is no higher than many other diets on the market. One finding that does recur throughout many of these studies is that overweight or obese diabetic patients lose weight, develop better control, or in some cases, revert to a nondiabetic state. This finding suggests that in obese or overweight dogs and cats, weight loss to achieve an ideal body condition may be the most effective modification toward achieving better glycemic control or in cats reverting to a nondiabetic state.

Minerals and Vitamins

Dogs and cats with diabetes are at risk for the following vitamin and mineral abnormalities: hypophosphatemia, hypokalemia, hyponatremia, hypochloremia, hypocalcemia, hypomagnesemia, and hypovitaminosis D. Generally, adequate control of the diabetes is sufficient to avoid these problems. Only when the primary disease is not controlled, diabetic ketoacidosis or a secondary problem develops, do these become more of a concern.

Chromium is an essential dietary trace element involved in carbohydrate and lipid metabolism. Chromium functions as a cofactor for insulin, and its presence is necessary for cellular uptake of glucose. The effect of oral chromium supplementation on glucose tolerance in healthy dogs and cats has been evaluated with conflicting results (Spears et al. 1998; Appleton et al. 2002). The only study done to determine the effect of oral chromium supplementation on glycemic control in IDDM dogs did not support any beneficial or harmful effects in the dosage range of 20–60 mcg/kg body weight/day (Schachter et al. 2001).

Food Type

Semi-moist pet foods or snacks should not be fed to diabetic pets. In dogs, postprandial blood glucose and insulin responses were highest in dogs fed semi-moist foods, compared to dry or canned foods (Holste et al. 1989). This is most likely due to the use of sucrose, fructose, and other simple carbohydrates in many semi-moist products. Cats do not appear to metabolize fructose, which may lead to intolerance, and polyuria due to fructosuria (Kienzle 1994).

Feeding Recommendations and Assessment

Remembering that every patient is unique, the optimal nutritional approach to managing a diabetic patient will vary from animal to animal. It is important that the diet fed to any diabetic is one that they will eat routinely. In general, for most cases a dietary change is not recommended at the time of diagnosis (unless a concurrent disease is present, such as pancreatitis). The animal should remain on its normal diet while undergoing stabilization. In patients that are difficult to regulate (and a secondary disease process has been ruled out), a diet change, either to a high-fiber diet or in some feline patients, a low-carbohydrate diet may be beneficial.

If one elects to increase the animal's fiber intake, this may be done by changing to a fiber-enhanced food or adding fiber to the animal's current diet. Fiber can be added as a mixed fiber source such as psyllium husk (e.g., Metamucil), 1–3 TB (1 TB = 14.79 mL) per day, soluble fiber such as guar gum (e.g., Benefiber), 2–4 tsp (1 tsp = 4.93 mL) per day or insoluble fiber such as wheat bran, 1–3 TB per day. Be aware that some fiber sources contain artificial sweeteners such as xylitol and should be avoided. Also using some canned food to deliver the fiber (by mixing them together) can be helpful especially in cats, but care should be taken to ensure that supplemental soluble fiber has "gelled" prior to feeding to prevent a potential choking hazard. Canned pumpkin can be used, but it only contains about half of the fiber per unit volume as psyllium. Pumpkin pie filling should not be used due to its sugar content. Start at the lower dose and titrate up as needed (larger amounts may be needed for large or giant breed dogs and smaller quantities for toy or small breeds). It can take a few weeks to see an effect, so patience is warranted.

It is also very important to remember that when carbohydrates are restricted in a diet, the calories supplied by fat will increase. This alteration can pose a serious and, in some cases, a life-threatening concern in diabetic patients with abnormalities in fat metabolism or pancreatitis.

If snacks and treats are included in the animal's feeding program, it is important that they are also consistent with regard to treat type and time of day offered, as well as low in soluble carbohydrates and fat.

Weight control and/or weight reduction is important in patients with diabetes. In overweight animals, a conservative weight loss protocol should be considered once the initial medical problems are controlled. When dogs and cats with diabetes lose weight, glucose tolerance improves. Weight loss in patients with IDDM can result in enhanced tissue sensitivity to insulin, necessitating lower daily insulin requirements. As a result, the patient should be carefully monitored and insulin doses adjusted as needed. During weight loss, frequent monitoring and caloric adjustment should be the norm, rather than the exception, in any patient with a disease process including diabetes (see Chapter 9).

HYPERLIPIDEMIA

Hyperlipidemia (also referred to as hyperlipoproteinemia) is a disturbance of lipid metabolism that results in an elevation in lipids in the blood, particularly triglycerides (triacylglycerides) and/or cholesterol (Johnson 2005). In the fasted state, hyperlipidemia is an abnormal laboratory finding and is caused by the accelerated synthesis or reduced degradation of lipoproteins. Among dogs and cats, the most clinically relevant type of hyperlipidemia is the finding of an excess concentration of triglycerides in the blood, hypertriglyceridemia (or hypertriacylglyceridemia). Hypercholesterolemia is a state of excess cholesterol in the blood. Unlike humans, most of the cholesterol in dogs is carried on high-density lipoproteins (HDL), the smallest lipoprotein (Johnson 2005). Patients with hypercholesterolemia do not have lipemic serum (unless triglycerides are concurrently elevated), because HDL particles do not refract the light due to their small size (Whitney 1992; Johnson 2005).

Classification and Etiology

Hyperlipidemic states can be classified as postprandial, primary or secondary. Postprandial hyperlipidemia is the most common hyperlipidemia in dogs and cats (Schenck and Elliott 2010). This is a normal physiological phenomena caused by an increase in the number of circulating chylomicrons. In some cases (depending upon the diet and amount of fat consumed) this can persist anywhere from 7 to 12 hours after a meal (Bauer 2004). However, even when a high-fat diet is consumed, serum triglycerides are not expected to exceed 500 mg/dL in a normal animal. Circulating chylomicrons carry only a fraction of the body's cholesterol, so meal consumption has little impact on cholesterol during the 6- to 12-hour postprandial period.

Primary causes of hyperlipidemia are either genetic or familial. The principal forms in dogs and cats are idiopathic hyperlipidemia of Miniature Schnauzers and hyperchylomicronemia of cats. The disease in Miniature Schnauzers is characterized by excess concentrations of circulating very-low-density lipoproteins (VLDL) with or without concurrent hyperchylomicronemia (Whitney, Boon et al. 1996; Jaeger et al. 2003; Xenoulis, Suchodolski et al. 2007). Familial hyperlipidemia in cats is caused by the production of an inactive form of lipoprotein lipase (LPL). Cats with this disease have increased fasting hyperchylomicronemia and elevations (slight) in VLDL (Backus, Ginzinger et al. 2001).

Secondary hyperlipidemia is associated with endocrine disorders (i.e., diabetes mellitus, hypothyroidism, and hyperadrenocorticism) or pancreatitis. Hypertriglyceridemia and hypercholesterolemia can be seen with hypothyroidism (Schenck, Donovan et al. 2004). In dogs with hypothyroidism, 88% had hypertriglyceridemia and 78% had hypercholesterolemia (Dixon et al. 1999). Hypertriglyceridemia is attributed to a decrease in lipid degradation, secondary to a reduction in LPL activity. Hypercholesterolemia is believed to result from impaired low-density lipoprotein (LDL) clearance from the circulation. It is postulated that in hypothyroid dogs an absolute deficiency in T_3 leads to an increase in the hepatic pool of cholesterol. Subsequently, more cholesterol is carried by LDL. In turn, LDL-receptor activity is also downregulated (Schenck 2006). Activation of hormone-sensitive lipase (HSL) by reduced insulin levels in diabetes mellitus causes the release of large quantities of free fatty acids into the bloodstream (Schenck and Elliott 2010). These excess free fatty acids are converted to VLDL particles by the liver and released back into the circulation. Additionally, insulin deficiency reduces the production of lipoprotein lipase, resulting in the reduced clearance of triglycerides from VLDL. In hyperadrenocorticism, a similar mechanism for hyperlipidemia has been proposed (Schenck and Elliott 2010). Stimulation of HSL releases free fatty acids into the bloodstream; these free fatty acids are packaged into VLDL by the liver and sent out into the circulation. Glucocorticoids inhibit LPL activity, thereby reducing the clearance of triglyceride-rich lipoproteins.

Clinical Signs and Diagnosis

Clinical signs associated with hyperlipidemia are variable and can be different in every patient. Some patients have no clinical signs and are diagnosed on routine blood work. The most common clinical presentations include vomiting (often intermittent), diarrhea, and/or abdominal discomfort. Triglyceride concentrations in excess of 1,000 mg/dL have also been associated with pancreatitis, cutaneous xanthomas, lipemia retinalis, seizures, peripheral nerve paralysis, and abnormal behavior (Schenck and Elliott 2010).

A blood sample to confirm hypertriglyceridemia should be obtained following a 12-hour fast. Serum should be submitted for analysis. Clear serum usually has a triglyceride concentration of less than 200 mg/dL. Serum turbidity generally begins to occur between 200 and 300 mg/dL, and lactescent serum is seen around 1,000 mg/dL (Bauer 1995; Johnson 2005).

Management and Assessment

Every attempt should be made to determine the underlying cause for the hyperlipidemia. Hyperlipidemia that occurs

secondary to an underlying metabolic disease often improves with correction or treatment of the problem (Whitney 1992; Johnson 2005). Dietary treatment of hyperlipidemia is a lifelong commitment, and the importance of nutritional management should be discussed and emphasized with the owner. It has been suggested that triglyceride concentrations greater than 500 mg/dL mandate treatment, even if the animal is asymptomatic, to prevent possible complications (Whitney 1992; Xenoulis and Steiner 2010). While primary hypercholesterolemia is associated with less severe complications, it is recommended that values greater than 750 mg/dL be treated (Schenck and Elliott 2010; Xenoulis and Steiner 2010).

Restriction of dietary fat is the foundation for the treatment of hypertriglyceridemia. Chylomicrons are produced from fat of dietary origin. The success of nutritional therapy is highly dependent upon the veterinarian's ability to select a product that is appropriate for the individual animal they are treating. One key piece of information that is frequently not considered or even obtained is the patient's diet history. A diet history should include not only the names and amounts of commercial food that the animal consumes but also snacks, treats, and dietary supplements. A diet should be selected that provides less fat than the animal is currently consuming. Most recommendations in the literature suggest feeding a diet that provides 20% of the calories or less from fat [metabolizable energy basis (ME)]. However, in many patients more severe restriction is often indicated, sometimes as low as 10% fat ME. The diet history is so critical because it helps the practitioner understand what degree and amount of restriction is indicated in every individual patient. For example, if the patient is currently consuming a diet that contains 25% of the calories from fat, restricting to 20% fat calories will unlikely have a significant impact. Treats should be restricted to low-fat treats as well. Baby carrots, rice cakes, salt-free nonfat pretzels are good human food alternatives. In addition to monitoring the fat intake, calorie intake should be carefully monitored as well. Caloric restriction is also indicated in overweight patients, as excess dietary energy increases VLDL production.

The authors have seen many animals placed on fiber-enhanced or weight loss foods based on the incorrect assumption that a high-fiber or weight loss diet is automatically a low-fat diet. It is also important to point out another common misconception. If a manufacturer makes a product in both a dry and canned form, it is often assumed that both contain approximately the same amount of fat. In some instances this is true; more often it is not. It is important to check the fat content of the diet directly from the manufacturer's website or product guide and provide clear guidelines to the client and support staff to ensure the patient receives the correct product.

Diets rich in omega-3 fatty acids have been used with some success to improve hypertriglyceridemia in humans and experimental animals by reducing the production of VLDLs (Illingworth et al. 1989; Froyland et al. 1995). Fish oils are poor substrates for triglyceride synthesizing enzymes and therefore are poor VLDL formers. In a study in healthy dogs, fish oil supplementation led to a significant reduction of serum triglyceride concentrations, suggesting that this supplement may play a role in the treatment of primary canine hypertriglyceridemia (LeBlanc et al., 2005; Xenoulis and Steiner 2010). However, studies evaluating the efficacy of fish oil supplementation in dogs and cats with clinically significant hyperlipidemia are lacking and clinical experience is limited (Xenoulis and Steiner 2010). In the veterinary literature, menhaden fish oil has been used by some authors (220–330 mg/kg BW daily) (Bauer 1995; Schenck and Elliott 2010). It is important to remember that the administration of fish oil will increase the amount of fat and total calories the animal is consuming, and one must account for this when assessing total dietary fat intake relative to meeting the goals for a particular patient.

Niacin has also been used in dogs (25–100 mg/day) to reduce triglyceride concentrations (Bauer 1995). It is proposed to act by decreasing fatty acid release from adipocytes and reducing the production of VLDL particles. It has been reported to reduce serum triglyceride concentrations in dogs for several months without any negative effects (Whitney 1992; Bauer 1995; Johnson 2005). Negative side effects of using niacin include vomiting, diarrhea, erythema, pruritis, convulsions, and death (Chen et al. 1938; Bauer 1995; Xenoulis and Steiner 2010).

Dietary fiber and niacin have also been used in humans to reduce cholesterol concentrations in an effort to prevent coronary artery disease. Coronary artery disease is extremely rare in dogs and cats, and the effect of fiber and niacin in reducing cholesterol levels is unknown. Dietary cholesterol comes from animal sources, so feeding a diet with reduced amounts of animal products may be helpful in reducing cholesterol concentrations. This can be accomplished in dogs using a vegetable-protein-based diet and in cats by selecting animal protein sources that are lower in fat and therefore potentially lower in cholesterol (e.g., lean fish, chicken, or pork).

The patient should be reevaluated in about four to eight weeks after starting the new, low-fat diet. If triglyceride concentrations have not decreased, several steps should be

taken. A diet history should be reevaluated to ensure that the patient is getting the correct diet, not receiving additional food sources within the household, nor getting access to food outside of the house (e.g., the neighbors, outdoor cat food, etc.). The patient's medical record should be reviewed to ensure an underlying disorder has not been overlooked. If triglyceride concentrations are not sufficiently reduced using a commercial product, a home-prepared diet can be formulated by a trained veterinary nutritionist to provide a ration that is lower in fat than the currently available veterinary therapeutic products (see Chapter 8).

HYPOTHYROIDISM AND HYPERADRENOCORTICISM IN DOGS

To date, there has been no link established between nutrition and the development of either hypothyroidism or hyperadrenocorticism in dogs. Currently, nutritional management is supportive and is used to address the clinical signs of polyphagia often leading to secondary weight gain and hyperlipidemia. The nutritional management of hyperlipidemia was discussed earlier in this chapter. Guidance on how to implement a successful weight loss plan is covered elsewhere in this book (see Chapter 9). However, there are potential strategies that one can employ to assist with polyphagia and prevent weight gain in these patients.

The first step is client education at the time of disease diagnosis. Weight gain occurs when calorie consumption exceeds energy expenditure. Dogs with both of these conditions may experience alterations on both sides of this equation. Many dogs with hypothyroidism or hyperadrenocorticism experience an increase in appetite while simultaneously reducing their energy expenditure. The result can be weight gain and constant hunger. Successfully treating the underlying disease may alleviate these signs. However, clients should be made aware of these concerns at the time the diagnosis is made and offered some advice on how to address them. In order to help abate hunger and prevent weight gain, one can recommend a diet with a low calorie density so that a similar or, in some cases, greater volume of food can be fed but still provide the same or a reduced number of calories. Diets that carry the label "lite" can be helpful in this regard due to their lower calorie density. Caution is warranted when evaluating products carrying the terms "lean" and "reduced" as they may not always have a low caloric density (see Chapter 6). Alternatively, one could consider instituting a high-fiber diet. There are several studies that have reported an increase in satiety in dogs fed high-fiber diets (Jewell and Toll 1996; Jackson et al. 1997; Weber et al. 2007). In some diets, the addition of fiber also reduces the caloric density of the food. However, it is important to remember that any recommendation should be done with the dog's diet history in mind in order to ensure that the new food provides fewer calories per gram than the current diet. Whenever possible, a few specific brands should be recommended to assist the owner in this process.

Additional strategies include the use of low-calorie treats, which may include commercial or human treats. Energy from treats should be included in the dog's total calorie count and should not exceed 10% of the total daily calories. It also helps if specific treats and amounts are recommended to assist the owner with this process. Feeding small, multiple meals or the use of food-dispensing cubes to delay the eating process may also aid with satiety.

FELINE HYPERTHYROIDISM AND IDIOPATHIC HYPERCALCEMIA

Unlike canine hypothyroidism or hyperadrenocorticism, a role for nutrition in the cause of both feline hyperthyroidism and idiopathic hypercalcemia has been proposed although nothing has been definitively identified at this time. Nutrition may also play a role in managing and modulating these diseases.

Hyperthyroidism

The etiology of feline hyperthyroidism is unknown at this time although many nutritional risk factors have been proposed. The consumption of canned diets has been cited in numerous studies to be a risk factor for thyroid disease in cats in the United States and the United Kingdom (Scarlett, Moise et al. 1988; Kass et al. 1999; Martin et al. 2000; Edinboro et al. 2004; Wakeling et al. 2009). One group hypothesized that the bisphenol A found in canned cat foods may be the goitrogenic substance of cause (Edinboro et al. 2004), although no further studies have been done to follow up on this proposal. Soybeans are another potential goitrogen used in feline diets (Court and Freeman 2002), and in one study in healthy cats, short-term administration caused an increase in serum T_4 and free T_4 concentrations (White et al. 2004).

The trace minerals selenium and iodine also have an effect on thyroid hormone concentrations in the cat. As selenium concentrations increase in the diet, serum T_3 concentrations also increase, and serum T_3 has been correlated with serum selenium concentrations (Wedekind, Howard et al. 2003; Zicker et al. 2010). Selenium concentrations are also reported to be higher in canned feline diets

compared to dry or canine diets (Zicker et al. 2010). Serum free thyroxine concentrations have been reported to be inversely related to dietary iodine concentrations (Tartellin et al. 1992). Iodine concentrations are reported to vary extensively in pet foods (Johnson et al. 1992). Although a recent study found no effect of iodine intake on total thyroxine (TT4) and total triiodothyronine (TT3) concentrations in adult cats, free thyroxine (FT4) was elevated in cats eating 8.8 mg I/kg of diet. The study suggests that the iodine requirement is lower than the current NRC recommended allowance (NRC 2006), but higher than the current Association of American Feed Control Officials (AAFCO 2010) allowance for this species (Wedekind, Blumer et al. 2009). Whether any of these alterations in thyroid hormone concentrations translates into abnormalities or thyroid disease long-term remains to be determined. Recently a new iodine restricted therapeutic feline diet was introduced. This diet is designed to reduce serum thyroxine concentrations in hyperthyroid cats. It is not currently recommended as a preventative diet.

In some cases a dietary change may not be warranted (e.g., those undergoing ablation, thyroidectomy, or radioactive iodine therapy), although the clinician should review the patient's diet history to ensure that a diet appropriate for the cat's life stage is being fed. In some cases, cats will experience significant weight loss and loss of lean body mass. Successful treatment of the hyperthyroidism should result in subsequent weight gain and restoration of lean body mass. In some cases, cats will also have chronic kidney disease or treatment of their hyperthyroidism will reveal underlying kidney disease. Patients should be monitored frequently and if kidney disease is diagnosed, an appropriate diet should be instituted (see Chapter 15).

Feline Idiopathic Hypercalcemia

At this time, no nutritional link or endocrinopathy has been identified as the cause of feline idiopathic hypercalcemia. Based on the authors' experience, hypercalcemia can be transient in some cats. In some, but not all, cases, dietary calcium restriction has resulted in a reduction of ionized calcium concentrations back to the normal range (A.J. Fascetti and S.J. Delaney, personal communication). A home-prepared diet is recommended if a reduction in dietary calcium is implemented, as currently no commercial diets are calcium-restricted. The use of a home-prepared diet also allows one to better regulate the vitamin D concentration as well (although higher dietary vitamin D levels closer to the AAFCO maximum have not been identified as a cause). The authors have had success in some cats that have been fed a home-prepared diet containing approximately 0.6 g Ca/Mcal, although it is unclear if the calcium restriction or some other variable is the cause for the positive response. Products containing high concentrations of vitamin D, such as organ meats and fish oil, should be avoided. Patients can be monitored using ionized calcium concentrations, in addition to the other parameters normally evaluated in any patient consuming a home-prepared diet (see Chapter 8). If no response is detected after a month, consideration should be given to returning the cat to its previous diet, as the patient may not be responsive to dietary calcium restriction.

SUMMARY

- Dietary fiber may have a role in the management of diabetes mellitus. Restricting dietary carbohydrates may be beneficial in some patients.
- Current scientific evidence does not support that carbohydrates in pet foods cause an increase in the incidence of obesity and diabetes mellitus.
- In obese or overweight dogs and cats, weight loss to achieve an ideal body condition may be the most effective modification toward achieving better glycemic control or in cats, reverting to a nondiabetic state.
- Successful management of hyperlipidemia is dependent upon selecting a diet that contains less fat than the diet the animal is currently consuming.
- Endocrinopathies that cause polyphagia can be managed with foods that are lower in energy density.
- A dietary change may be indicated in cats with hyperthyroidism; however, if concurrent kidney disease is present or unmasked with treatment, an appropriate renal failure therapeutic diet should be fed.
- Although the etiology is unknown for feline idiopathic hypercalcemia, a home-prepared, calcium-restricted diet should be considered.

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Nutritional Management of Cardiovascular Diseases

18

Lisa M. Freeman and John E. Rush

Cardiac disease is one of the most common disorders in both dogs and cats, affecting 11% of all dogs and up to 20% of some feline populations (Buchanan 1999; Cote et al. 2004; Lund et al. 1999; Paige et al. 2009). Although none of the common cardiac diseases in dogs and cats currently are easily corrected (although surgical replacement or repair of the mitral valve is possible where cardiopulmonary bypass is available), these diseases can be successfully managed medically. Medical therapy of cardiac disease has improved in recent years, with newer and more effective drugs, but medical therapy still is only palliative, with the goal of controlling clinical signs, slowing the progression of disease, and improving quality of life. Maintaining good quality of life is particularly important in dogs and cats, for whom owners often prefer quality of life to "quantity" of life (Oyama et al. 2008).

One key component of medical therapy is nutrition. Careful attention to the diet of animals with cardiac disease is critical for the optimal treatment of these patients. In the past, the goal of nutritional management for animals with cardiac disease was purely symptomatic and focused only on sodium restriction. This was primarily due to the limited number of medications available for treatment, and in that situation, sodium restriction was beneficial for reducing fluid accumulation in animals with congestive heart failure (CHF). Now, with more effective medications available for use in dogs and cats, severe sodium restriction is not required in most animals with cardiac disease. The current emphasis in nutritional management for these patients is on providing the optimal number of calories for the individual animal, avoiding nutritional deficiencies and excesses, and gaining potential benefits from pharmacologic doses of certain nutrients. Optimal nutrition may reduce the number or doses of medications an animal requires, reduce complications, improve quality of life, and may slow the progression of the disease. Therefore, nutrition has an integral role in the medical management of animals with cardiac disease.

FEEDING THE CAT WITH CARDIAC DISEASE

Hypertrophic cardiomyopathy (HCM) currently is the most common form of cardiac disease in cats but other forms of cardiomyopathy (i.e., dilated, restrictive, or unclassified) and other diseases (e.g., heartworm disease, pericardial disease) also can occur. Cardiac disease often is perceived as a relatively uncommon disease in cats but one publication reported that 21% of overtly healthy cats screened had a cardiac murmur (Cote et al. 2004). Of the cats with murmurs that subsequently underwent echocardiography, 86% had structural cardiac disease, primarily HCM (Cote et al. 2004). A more recent study found that 16 of 103 apparently healthy cats had cardiomyopathy (Paige et al. 2009). Thus, cardiac disease appears to be a very common disease in the feline population and regardless of the cause often leads to CHF, arterial thromboembolism (ATE), syncope, or sudden death.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is a disease associated with reduced myocardial contractility and dilation of all four cardiac chambers. This disease most often results in CHF. Dilated cardiomyopathy once was one of the most

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common heart diseases in cats until the publication of a paper associating feline DCM and taurine deficiency, with reversal of cardiomyopathy following taurine supplementation (Pion et al. 1987). Since that time, the dietary taurine content of commercial cat foods has increased, and there has been a dramatic reduction in the incidence of feline DCM.

Dilated cardiomyopathy is occasionally still seen in cats today, but most current cases are not taurine deficient and a taurine-independent variant of DCM is causative in most cases. Still, owners of cats with DCM should be carefully questioned about the cat's diet as cats that have been fed poor-quality, homemade, vegetarian, or otherwise unbalanced diets are at risk for taurine deficiency. One study, for example, found that two commercial vegetarian diets that claimed to be complete and balanced contained only 18–24% of the Association of American Feed Control Officials (AAFCO) minimum for taurine for adult cat maintenance (Gray et al. 2004). All cats with DCM should have plasma and whole blood taurine concentrations analyzed as part of the diagnostic workup and taurine should be administered (125 to 250 mg/cat PO q 12 h) until results are available. If the cat is eating an unconventional diet, the owner also should be counseled to switch to a nutritionally balanced animal-protein-based commercial cat food. Cats with taurine deficiency-induced DCM often have dramatic reversal of myocardial function after supplementation if their CHF can be successfully controlled and stabilized for at least 2 to 3 weeks. Cats with DCM that is unrelated to taurine deficiency have a less promising outcome.

Hypertrophic Cardiomyopathy

Feline HCM is characterized by left ventricular hypertrophy, impaired diastolic filling, and often secondary left atrial enlargement (Fox 1999a; Kittleson and Kienle 1998). In cats with HCM, CHF and ATE are common clinical manifestations, with ATE reportedly developing in up to 48% of affected cats (Atkins et al. 1992; Fox 1999; Kittleson and Kienle 1998; Rush, Freeman et al. 2002; Tilley 1975; Tilley and Weitz 1977). The most common site of ATE in cats is the terminal aorta, resulting in hind limb paresis/paralysis, but other limbs and other sites can be affected less frequently (Fox 1999; Rush, Freeman et al. 2002; Kittleson and Kienle 1998). Other clinical manifestations of HCM in cats include syncope, arrhythmias, and sudden death (Fox 1999; Rush, Freeman et al. 2002; Kittleson and Kienle 1998). The median survival time for cats with HCM is less than 2 years, with cats presenting for CHF or ATE having even shorter survival times (Rush, Freeman et al. 2002). Unlike in people, in whom over 400 mutations in sarcomeric proteins are known, no disease-causing mutations have been identified in the majority of cats with HCM, except for the myosin binding protein C mutation in Maine Coon and Ragdoll cats (Meurs, Sanchez et al. 2005; Meurs Norgard et al. 2007). Until genetic screening and prevention are possible, management of cats with HCM is limited to a combination of medication and diet.

For cats with HCM, the dietary management depends upon the stage of disease. For cats with HCM but no clinical signs [International Small Animal Cardiac Health Council (ISACHC) Stages 1a or 1b], no dietary modifications currently are proven to be beneficial, although research is being conducted in order to determine efficacious nutritional strategies for this stage. This would be especially useful considering the lack of a proven drug therapy for asymptomatic cats. Nonetheless, this is an ideal time to begin talking to the owner about the animal's overall dietary patterns (i.e., the pet food, treats, table food, and medication administration) and achieving ideal body weight/body condition, as it is easier to institute dietary modifications before clinical signs have arisen. Mild sodium restriction (<100 mg/100 kcal) is recommended although further research is needed to determine the optimal dose and timing for sodium restriction in cats with cardiac disease. Severe sodium restriction (<50 mg/100 kcal) is not recommended as this can cause early and prolonged activation of the renin-angiotensin-aldosterone (RAA) system (Pedersen 1996; Freeman, Rush et al. 2006).

When cats with HCM develop mild-moderate CHF (ISACHC Stage 2), moderate sodium restriction (i.e., <80 mg Na/100 kcal) is indicated in conjunction with medical therapy although severe sodium restriction still is usually unnecessary. Anorexia becomes more of a problem in cats with CHF. In one study, 38% of cats with cardiac disease had a current or past history of anorexia (i.e., either a reduction or cessation of food intake), and cats with CHF were significantly more likely than cats without CHF to be anorectic (Torin et al. 2007). Anorexia can be caused by medication side effects (e.g., azotemia secondary to ACE inhibitors or excessive diuretic use) so careful monitoring of drug doses and the serum biochemistry profile for alterations in BUN, creatinine, and electrolytes is important. Providing a more palatable diet can help to improve appetite (e.g., switching from a dry food to a canned food or vice versa, changing to a different brand, warming the food, adding small amounts of unsalted meat or fish (e.g., 1–2 tsp/cat/meal), or prescribing a balanced

cooked homemade diet formulated by a veterinary nutritionist). Supplementation with fish oil, which is high in n-3 fatty acids, can decrease inflammatory cytokine production and improve appetite in some cats with CHF (Freeman, Rush et al. 1998; see n-3 fatty acid section below).

Thiamine deficiency is known to be a cause of cardiomyopathy in people but there has been little investigation into the role of B vitamins as a cause of heart disease in cats (or dogs). Anorexia can contribute to B vitamin deficiencies, as can increased urinary losses of water soluble vitamins due to diuretic use. One recent human study reported that 33% of CHF patients were thiamine deficient (Hanninen et al. 2006). Research has shown that plasma concentrations of vitamins B6, B12, and folate were significantly lower in cats with cardiomyopathy than in healthy controls, an effect that was unrelated to diet or furosemide use (Hohenhaus, Simantov, Fox, et al. 2000; McMichael et al. 2000). Therefore, animals with cardiac disease (at least those receiving diuretics) may have higher B vitamin requirements. Although most commercial feline diets contain relatively high levels of water soluble vitamins, B vitamin supplementation may be useful for cats with CHF, particularly those receiving large doses of diuretics.

In severe CHF, greater restriction of dietary sodium (<50 mg) may allow lower dosages of diuretics to be used to control clinical signs; however, it is critical that adequate food intake is maintained. Therefore, compromises often must be made between the "ideal diet" and one that the cat will eat; at this stage, anorexia can be a significant problem. Nonetheless, maintaining at least mild sodium restriction is recommended. In these situations, feeding tubes can be an important consideration to address calorie and other nutrient needs. There also is a higher risk for potassium and magnesium abnormalities in cats with severe CHF because of the high doses of diuretics usually required, so monitoring of electrolytes is important for optimal care.

Hypertension

Traditionally, low-sodium diets have been recommended for cats (and dogs) with hypertension. This has been based primarily on data from rodents or people. Idiopathic hypertension is much less common than essential hypertension in people. In veterinary patients, high blood pressure is the result of "white coat hypertension" or is secondary to medications, renal disease, or other medical disorders in more than 80% of cases (Brown et al. 2007). In the case of secondary hypertension due to systemic diseases, medical and nutritional treatment of the underlying disease is a priority. In many cases, sodium restriction may also be a part of the recommended nutrient modifications for that disease (e.g., chronic kidney disease).

Even in people, there is much controversy over the relative role of sodium in the development of hypertension and the degree of sodium restriction that should be recommended. The current recommendations for people with hypertension are a combination of pharmacologic treatment and lifestyle changes, including a reduced-sodium diet (Chobanian et al. 2003). However, other nutrients, such as potassium, may play as important a role in hypertension as sodium.

Despite concerns over high-sodium diets in animals with hypertension, studies in normal cats and in cats and dogs with experimentally induced kidney disease have shown no detrimental effect on blood pressure (Buranakarl et al. 2004; Cowgill et al. 2007; Greco et al. 1994; Hansen et al. 1992; Kirk et al. 2006; Xu, Laflamme, and Long 2009). However, the effects of sodium restriction in animals with naturally occurring idiopathic hypertension are not known. Currently, the ACVIM Consensus Statement on Systemic Hypertension recommends "avoiding high dietary sodium chloride intake in hypertensive animals but does not recommend that a specific effort be made solely to restrict dietary sodium chloride intake" (Brown et al. 2007). Currently, medical therapy should be the primary method used to achieve control of blood pressure; however, optimal treatment of any underlying disease is important and may include modification of dietary sodium intake.

FEEDING THE DOG WITH CARDIAC DISEASE

Cardiac disease is one of the most common health problems seen in dogs, with approximately 95% of affected dogs having adult-onset (acquired) cardiac disease. For dogs with adult-onset disease, the majority (75–80%) have endocardiosis [commonly referred to as chronic valvular disease or CVD (Buchanan 1999)]. Another 5–10% have DCM, and the remaining dogs with cardiac disease have pericardial disease, endocarditis, primary arrhythmias, or heartworm disease (Buchanan 1999). In dogs, small- to medium-sized dog breeds are predisposed to CVD, while DCM is the most common cause of CHF in large breed dogs.

As in cats, the major differences for nutritional modifications are based on stage of cardiac disease, but there are some specific issues relevant for dogs with DCM, as noted below.

Asymptomatic Disease (ISACHC Stages 1a and 1b)

The sympathetic nervous system and the RAA system become increasingly activated as heart disease progresses.

Thus, severe sodium restriction in animals with early heart disease could theoretically be detrimental by early and excessive activation of the RAA system (Pedersen 1996; Freeman, Rush et al. 2006). The results of one study reported that a low-sodium diet fed to dogs with asymptomatic CVD resulted in increased aldosterone concentrations and heart rate, with no improvement in cardiac size or function (Freeman, Rush et al. 2006). Because of the potential detrimental effects and lack of documented benefits of severe sodium restriction in asymptomatic disease, the authors recommend only mild sodium restriction (<100 mg/100 kcal) in asymptomatic heart disease (ISACHC Stages 1a and 1b). However, as in cats, this is an opportune time to begin educating the owner about the animal's overall dietary patterns—the pet food, treats, table food, and how medications are administered—as it is generally much easier to institute dietary modifications at this stage, before the dog develops clinical signs of CHF.

In addition to mild sodium restriction in animals with asymptomatic cardiac disease, the other main goal is to achieve or maintain optimal body condition. Animals with cardiac disease may be overweight or obese, particularly those in the asymptomatic stages. Obesity can exacerbate signs of cardiac disease, and weight loss in severely obese animals with cardiac disease usually helps to reduce clinical signs (e.g., improved ability to ambulate, better exercise tolerance, less dyspnea). Weight reduction programs can be challenging and run a high risk of failure without carefully planning a comprehensive program and providing regular monitoring and adjustment. Therefore, a carefully designed and monitored weight loss program is essential for success (see Chapter 9).

Finally, there is a great deal of potential for benefit with nutritional modification in the dog with asymptomatic disease. One study compared a moderately reduced sodium cardiac diet that was enriched with n-3 fatty acids, antioxidants, arginine, taurine, and carnitine to a placebo diet in dogs with asymptomatic CVD (Freeman, Rush et al. 2006). The cardiac diet increased circulating levels of key nutrients (e.g., antioxidants, n-3 fatty acids) and also reduced cardiac size, an effect that did not appear to be the result of sodium restriction. Future studies will help to increase our understanding of the role for nutritional modification in this early stage of disease.

Mild to Moderate CHF (ISACHC Stage 2)

Cardiac Cachexia

When CHF develops, additional nutritional concerns arise for the dog with cardiac disease. Maintaining optimal body condition is of primary importance in the animal with CHF. Although obesity still can be present at this stage, animals with CHF more commonly begin to demonstrate weight loss. This weight loss is known as cardiac cachexia and is unlike that seen in a healthy animal. A healthy animal that receives insufficient calories to meet energy requirements loses primarily fat. In an animal with CHF that receives insufficient calories, the primary tissue lost is lean body mass (Freeman and Roubenoff 1994). This loss of lean body mass has deleterious effects on strength, immune function, and survival (Anker et al. 1997; Freeman and Roubenoff 1994). Therefore, it is important to recognize cachexia in its earliest stages when there is the greatest opportunity to have a positive impact. Cardiac cachexia is not only the classical picture of the emaciated, end-stage patient; cachexia actually occurs on a spectrum of severity [Figs. 18.1(a) and 18.1(b)].

In the early stages, cachexia can be very subtle and may even occur in obese animals (i.e., an animal may have excess fat stores but still lose lean body mass). Loss of lean body mass is usually first noted in the epaxial, gluteal, scapular, or temporal muscles (Figs. 18.1[a] and 18.1[b]). Cardiac cachexia typically does not occur until CHF has developed but can occur with any underlying cause of CHF (e.g., DCM, CVD, congenital heart diseases). Cardiac cachexia is a common finding in dogs with CHF and is a multifactorial process caused by anorexia, increased energy requirement, and an increased production of inflammatory cytokines (Freeman and Roubenoff 1994). The cytokines, tumor necrosis factor (TNF), and interleukin-1 (IL-1) are elevated in people, dogs, and cats with CHF (Freeman, Rush et al. 1998; Levine et al. 1990; Meurs, Fox et al. 2002). These cytokines cause anorexia, increase energy requirements, and increase the catabolism of lean body mass (Freeman and Roubenoff 1994). In addition, TNF and IL-1 also cause cardiac myocyte hypertrophy and fibrosis and have negative inotropic effects (Mann 2002).

Managing dogs with cardiac cachexia can be challenging but is more successful when identified and addressed early in the process. The authors assess all animals with CHF for the presence of cachexia and grade it on a 5-point scale, where 0 = no muscle loss, 1 = mild muscle loss, 2 = moderate muscle loss, 3 = marked muscle loss, and 4 = severe muscle loss (Freeman, Rush et al. 1998). The nutritional keys to managing cachexia are ensuring adequate calorie and protein intake and modulating cytokine production. Anorexia, either a complete or partial loss of appetite, is extremely common in cardiac disease, particularly in dogs with CHF, with a prevalence between 34% and 84% of dogs with cardiac disease (Freeman, Rush,

Fig. 18.1. (a) Photo of dog with dilated cardiomyopathy and mild-moderate congestive heart failure (International Small Animal Cardiac Health Council Stage 2). This dog also has moderate cachexia (cachexia score = 2 on a 0–4 scale). Cardiac cachexia is a process in which there is a progressive loss of lean body mass and which may be subtle in the early stages. Muscle loss can first be detected in the epaxial, gluteal, temporal muscles, and muscles of the scapular region. (b) The same dog with dilated cardiomyopathy and more advanced congestive heart failure, now with severe cardiac cachexia (cachexia score = 4 on a 0–4 scale). It is ideal to identify cachexia in its early, subtle stages in which intervention is likely to be more successful.

Cahalane, Kaplan, Markwell 2003; Mallery et al. 1999). After CHF develops, complete anorexia may not develop but owners often note changes in appetite, such as reductions in food intake, changes in food preferences, or "cyclical" appetite (i.e., dogs will eat one food well for several days and then refuse it). One of the most important issues for managing anorexia is to optimize medical therapy. A reduction in food intake in an animal that previously has been eating well may be an early sign of worsening CHF or a need for medication adjustment. Medication side effects, such as digoxin toxicity or azotemia secondary to ACE inhibitors or overzealous diuretic use also can cause anorexia. Providing a more palatable diet can help to improve appetite (e.g., changing to a different brand or form of food, having a balanced home-cooked diet formulated by a veterinary nutritionist). Smaller, more frequent meals also may increase food intake, as can flavor enhancers (i.e., foods added to the dog food to increase palatability), such as yogurt, maple syrup, or applesauce. Dogs with cardiac disease often appear sensitive to food temperature and may have specific preferences so experimentation with foods at different temperatures may be helpful. Feeding the dog on a dinner plate, rather than the usual dog food bowl, or feeding in a different place in the house also may increase food intake. Modulation of cytokine production also can be beneficial for managing cardiac cachexia. Supplementation of fish oil, which is high in n-3 fatty acids, can decrease inflammatory cytokine production and improve cachexia and food intake (see the n-3 fatty acid section below). A reduction of IL-1 has been correlated with survival in dogs with CHF (Freeman et al. 1998).

Because loss of lean body mass occurs in animals with CHF, it is critical to ensure intake of protein in addition to calories. Protein restriction was recommended for dogs with CHF in the 1960s because of concerns over the "metabolic load" on the kidneys and liver. However, restricting protein is not recommended in animals with CHF because it can contribute to lean body mass loss and malnutrition. Therefore, animals with CHF should not be protein restricted, unless they have concurrent advanced renal disease (see Chapter 15). Some of the diets designed for dogs with cardiac disease are very low in protein. Similarly, renal diets, which are too protein restricted for most dogs with CHF, have been recommended by some authors for cardiac disease because these diets often (but not always) are moderately sodium restricted. Unless indicated for concurrent disease, high-quality protein should be fed to dogs to at least meet the AAFCO minimum of 5.14 g/100 kcal, although higher protein intake may be beneficial, particularly in animals with significant muscle loss.

Cardiac cachexia has many deleterious effects but recent studies have also shown that obesity may have differential effects in otherwise healthy dogs compared to those with CHF. While obesity is a risk factor for heart failure, obesity may actually be associated with a protective effect once CHF is present—this is known as the obesity paradox. Multiple studies in people have been published in the past several years suggesting a beneficial effect of overweight and obesity in various populations of human patients with CHF, including a meta-analysis that concluded that obesity and overweight were associated with lower all-cause and cardiovascular mortality. Underweight patients had a higher risk of death (Oreopoulos et al. 2008). Although there are a number of hypothesized reasons for the obesity paradox, the benefit of obesity in CHF is likely due more to a *lack* of cachexia, rather than to the obesity per se, given the adverse effects associated with cachexia. The obesity paradox also has been demonstrated in dogs with CHF (Slupe et al. 2008).

n-3 Fatty Acids

Fat serves as a source of calories and essential fatty acids but fatty acids also can have significant effects on immune function, inflammatory mediator production, and hemodynamics. Most pet foods contain primarily n-6 fatty acids (e.g., linoleic acid, arachidonic acid) and are low in the long-chain n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA). In dogs or cats that consume a typical diet, long-chain n-3 fatty acids generally are found in low concentrations in the cell membrane compared to the n-6 fatty acids; however, concentrations can be increased by the consumption of foods or supplements high in n-3 fatty acids. There are a number of benefits of increased dietary n-3 fatty acid intake (Freeman, 2010). One is that breakdown products of the n-3 fatty acids (eicosanoids) are less potent inflammatory mediators than eicosanoids derived from n-6 fatty acids. Production of TNF and IL-1 is directly reduced by n-3 fatty acids, and n-3 fatty acid supplementation has been shown to reduce the muscle loss in dogs with CHF and, in some animals, to improve appetite (Freeman, Rush et al. 1998). Another potential benefit is that n-3 fatty acids have been shown to have antiarrhythmic effects in a variety of species including Boxers with ventricular arrhythmias (Smith et al. 2007).

Although an optimal dose of n-3 fatty acids has not been determined, the authors currently recommend a dosage of fish oil to provide 40 mg/kg EPA and 25 mg/kg DHA for

animals with anorexia or cachexia. Unless the diet is one of a few specially designed therapeutic diets, supplementation will be necessary to achieve this n-3 fatty acid dose. When recommending a supplement, it is important to know the exact amount of EPA and DHA in the specific brand of fish oil since supplements vary widely. The most common formulation of fish oil, however, is 1 g capsules that contain approximately 180 mg EPA and 120 mg DHA. At this concentration, fish oil can be administered at a dose of one capsule per 10 pounds of body weight to achieve the authors' recommended EPA and DHA dosage. Fish oil supplements should always contain vitamin E as an antioxidant, but other nutrients should not be included to avoid toxicities. Cod liver oil should not be used to provide n-3 fatty acids at this dose, because it can contain high levels of vitamins A and D, which can result in toxicity. Inefficient hepatic elongation of plant-based n-3 fatty acids (i.e., α-linolenic acid) to EPA and DHA in dogs (and particularly in cats) make flax seed oil a much less effective source of n-3 fatty acids for these species (Bauer 2007). In addition, ventricular arrhythmias in dogs were not significantly reduced by flax seed oil supplementation, as they were with fish oil (Smith et al. 2007). It should be noted that the authors believe that the dose cited above is impactful regardless of the underlying n-6 fatty acid content of the diet assuming it is a "typical" maintenance adult pet food.

Sodium

Studies in the 1960s (performed at a time when few cardiac medications were available) demonstrated that low-sodium diets resulted in reduced congestion in dogs with CHF (Pensinger 1964). However, current medical therapy for dogs with CHF may make severe sodium restriction less critical for these patients. While there have been no studies documenting the benefit of sodium restriction on survival or quality of life in dogs with CHF, studies have shown that a low-sodium diet (40 mg/100 kcal) reduced cardiac size in dogs with CHF compared to a diet containing 70 mg/100 kcal (Rush, Freeman et al. 2000). In dogs with ISACHC Stage 2, the authors recommend moderate sodium restriction (i.e., <80 mg/100 kcal).

Potassium and Magnesium

Potassium and magnesium are nutrients of concern in cardiac patients because depletion of these electrolytes can cause cardiac arrhythmias, decreased myocardial contractility, muscle weakness, and can potentiate the adverse effects of cardiac medications. Many of the medications used in animals with CHF, such as loop diuretics (e.g., furosemide) and thiazide diuretics (e.g., hydrochlorathiazide) can predispose a patient to hypokalemia or hypomagnesemia. Inadequate dietary intake of potassium or magnesium also predisposes animal to hypokalemia or hypomagnesemia. However, it is also important to note that hyperkalemia is just as likely as hypokalemia given the increased use of angiotensin converting enzyme (ACE) inhibitors, which result in renal potassium-sparing. Spironolactone, an aldosterone antagonist and potassium-sparing diuretic, also can cause hyperkalemia. Finally, some commercial cardiac diets are high in potassium, which can exacerbate hyperkalemia.

Serum potassium should be routinely monitored in CHF patients, particularly in those receiving an ACE inhibitor, spironolactone, or high diuretic doses. Serum magnesium concentrations also should be measured but clinicians should be aware that serum magnesium concentrations are a relatively poor indicator of total body stores. Nonetheless, serial evaluations in an individual patient may be useful, especially in patients with arrhythmias or in those taking high doses of diuretics. Diets range greatly in their potassium content so if hypo- or hyperkalemia are present, a diet with a higher or lower potassium content, respectively, should be selected. Diets high in magnesium may be beneficial in a hypomagnesemic animal.

Antioxidants

Antioxidants have received a great deal of attention in the popular press in terms of preventing and treating coronary artery disease, although enthusiasm has waned in recent years as the result of an increasing number of negative reports. However, antioxidants may play a role in canine and feline cardiac diseases. Reactive oxygen species cause cellular damage, have negative inotropic effects, and perpetuate an inflammatory response. Normally, the reactive oxygen species being produced as a result of normal oxygen metabolism are balanced by endogenously produced antioxidants. However, an imbalance can arise if there is either increased oxidant production or inadequate endogenous antioxidant protection. Recent studies have shown that in dogs with CHF due to either DCM or CVD there is an imbalance between oxidant production and antioxidant protection, particularly as CHF progresses to more advanced stages (Freeman, Brown et al. 1999; Freeman, Rush et al. 2005). Supplemental antioxidants are now included in many commercial veterinary diets, including at least one cardiac diet, and can increase circulating antioxidant concentrations and reduce oxidation (Freeman, Rush et al. 2006). The effect of antioxidant supplementation in animals with CHF is not yet known; however, this may hold promise for the future.

Arginine

Arginine is an essential amino acid for both dogs and cats. In addition, it is a precursor for nitric oxide, an endogenous vascular smooth muscle relaxant. Nitric oxide is synthesized from L-arginine and oxygen and is catalyzed by one of the three forms of nitric oxide synthase (NOS), inducible NOS (iNOS), endothelial NOS (eNOS), or neuronal NOS (nNOS). Both eNOS and nNOS are constitutive forms and are always produced in low levels. Endothelial NOS is required for the maintenance of normal vascular tone, but iNOS is induced by inflammatory mediators such as TNF, IL-1, and free radicals. High levels of iNOS and resulting nitric oxide are induced as part of the inflammatory response and also have negative inotropic effects. Circulating nitric oxide is elevated in people and cats with cardiac disease and in at least one study of dogs with cardiac disease [although another study showed reduced concentrations in dogs with CVD (de Laforcade et al. 2003; Freeman, McMichael et al. 2003; Pedersen, Schutt et al. 2003)]. But, while iNOS is upregulated in CHF, producing high circulating levels of nitric oxide, eNOS is actually downregulated, thus reducing endothelium-dependent vasodilation (Kubo et al. 1991). Endothelial dysfunction occurs as a result and contributes to exercise intolerance and poor quality of life in humans with CHF (Katz 1995). Arginine supplementation has been shown to improve endothelial dysfunction in people with CHF (Hambrecht et al. 2000). Nitric oxide is difficult to measure but noninvasive techniques to assess endothelial function have recently been validated (Puglia et al. 2006), and studies are underway to determine the extent of endothelial dysfunction in dogs with CHF and whether nutritional interventions can alter this response.

Severe or Refractory CHF (ISACHC Stage 3a or 3b)

In severe CHF, greater restriction of dietary sodium (<50 mg/100 kcal) may allow lower dosages of diuretics to be used to control clinical signs. At this stage of disease, cardiac cachexia invariably occurs so it is critical to ensure adequate calorie and protein intake. This can be a challenge as appetite in severe CHF is often cyclical, and owners should be warned that appetite can be highly variable. Another issue to consider is that anorexia in an animal that has been eating can be an early sign of worsening disease or the need for medication adjustment and should trigger a reevaluation. In addition to optimization of medical therapy, the authors recommend multiple choices for appropriate pet foods, a homemade diet, or even single food items (e.g., home-cooked meat, low-sodium breakfast cereal, or Clif® Bars) that can increase calorie intake without exacerbating the underlying disease. Palatability enhancers also can be very helpful for dogs with severe CHF (e.g., cooked meat without sauce or spices, yogurt, applesauce, ice cream, or maple syrup). Encouraging the owner to try offering foods at different temperatures may increase food intake in some animals (e.g., warmed vs. room temperature vs. cold). Supplementation with n-3 fatty acids also can be beneficial in some animals in which appetite is poor. Other tips that may increase food intake include providing smaller, more frequent meals; feeding the recommended diet from a dinner plate; or putting the recommended diet into a treat jar.

Canine DCM

Supplementation of certain nutrients, either in the diet or in the form of dietary supplements, may have benefits for all dogs and cats with cardiac disease. The use of dietary supplements is more common in dogs as there are more recommendations in this species and because pills are more easily administered to dogs than to cats. Although some studies have been conducted on these nutrients, the supporting data are not yet robust enough to make firm recommendations for most of these nutrients. However, because many of these have potential benefits and/or are already being used by owners, they are discussed below. With dietary supplements, both the cost and number of medications and supplements that are administered to dogs with DCM should be considered in order to maximize compliance. In addition, it is important for both the veterinarian and the owner to be aware of issues of safety, efficacy, and quality control for dietary supplements (see Chapter 5). Veterinarians should always specifically ask owners of dogs (and cats) with cardiac disease if they are administering dietary supplements as this information is rarely volunteered by the owner. However, 31% of dogs and 13% of cats with cardiac disease receive dietary supplements (Freeman, Rush et al. 2003; Torin et al. 2007).

Taurine

While taurine is an essential nutrient for cats (i.e., they require dietary taurine), dogs are thought to be able to synthesize adequate amounts of taurine endogenously so it is not classified as an essential nutrient for dogs. Dilated cardiomyopathy in dog breeds that are at highest risk for

the disease (e.g., Doberman Pinschers, Boxers) does not appear to be related to taurine deficiency, but taurine deficiency has been documented in some dogs with DCM of certain breeds, such as the American Cocker Spaniel, Newfoundland, Portuguese Water dog, and Golden Retriever (Alroy, Rush, Sarkar 2005; Backus, Cohen et al. 2003; Fascetti et al. 2003; Freeman, Rush et al. 2001; Kittleson, Keene et al. 1997; Kramer et al. 1995). Taurine deficiency may occur more commonly in certain breeds because of higher requirements or breed-specific metabolic abnormalities, but diet also may play a role. Very-low-protein diets, certain lamb meal and rice diets, and some high-fiber diets have been associated with taurine deficiency, although the exact role of diet is not yet known (Backus, Cohen et al. 2003; Backus, Ko et al. 2006; Delaney et al. 2003; Fascetti et al. 2003; Freeman, Rush et al. 2001; Kittleson, Keene et al. 1997; Ko et al. 2007; Kramer et al. 1995; Sanderson et al. 2001; Spitze et al. 2003; Torres et al. 2003).

Although at least one small study has shown some improvements in clinical or echocardiographic parameters in taurine-deficient dogs supplemented with taurine, the response generally is not as dramatic as is seen in cats with taurine-deficiency-induced DCM (Kittleson, Keene et al. 1997). Ongoing research in this area will help veterinarians to better understand this disease and to make better recommendations in the future; however, the authors currently recommend measuring plasma and whole blood taurine concentrations in dogs with DCM that are of high risk (e.g., Cocker Spaniel, Newfoundland, Golden Retriever) or atypical (e.g., Corgi, Bassett Hound) breeds. In addition, taurine concentrations should be measured in dogs with DCM that are eating lamb meal and rice-based diets, vegetarian diets, high-fiber diets, or diets that are highly protein restricted. Although the extent of benefits of supplementation is not yet clear, the authors recommend taurine supplementation until plasma and whole blood taurine concentrations are available. The optimal dose of taurine for correcting a deficiency has not been determined. A dose of 250–1000 mg q 8–12 h is recommended, although the exact dose required for repletion of taurine deficient dogs is not known.

L-Carnitine

L-Carnitine is a water-soluble, vitamin-like compound synthesized from the amino acids lysine and methionine that is critical for myocardial energy production. Carnitine deficiency syndromes can be associated with primary myocardial disease in people, and carnitine deficiency was reported in a family of Boxers (Keene 1992). Since that time, L-carnitine has been supplemented in some dogs with DCM but no blinded prospective studies have been conducted in dogs. Even if primary carnitine deficiency is not present, a secondary deficiency of carnitine may develop in CHF. This has been demonstrated in a rapid-pacing model of CHF in dogs (McEntee et al. 2001; Pierpont et al. 1993). In this case, supplementation still may be beneficial by improving myocardial energy metabolism. This may be the reason for benefits shown in some, but not all, human studies. One of the limitations on progress in the study of carnitine deficiency is that myocardial concentrations must be measured to document a deficiency since plasma concentrations are often normal even in the face of myocardial deficiency.

L-carnitine supplementation has few side effects, but it is a relatively expensive dietary supplement. Some commercial cardiac diets also are enriched in carnitine. The authors offer the option of L-carnitine supplementation to owners of dogs with DCM, especially Boxers, but do not consider it essential. The minimum or optimal dose of L-carnitine necessary to replete a dog with low myocardial carnitine concentrations is not known, but the dose that has been recommended is 50–100 mg/kg PO q 8 h.

Coenzyme Q10

Coenzyme Q10 is a coenzyme for multiple mitochondrial enzymes and so is involved in myocardial energy production. This, in addition to its antioxidant properties, has made it a compound of interest for CHF, particularly for DCM. The purported benefits of supplementation include correction of a coenzyme Q10 deficiency, improved myocardial metabolic efficiency, and increased antioxidant protection. Studies in people with CHF have yielded conflicting results (Keogh et al. 2003; Munkholm et al. 1999; Sacher et al. 1997; Watson et al. 1999), and although no controlled studies in dogs with spontaneously occurring cardiac disease have been published, there is one study of dogs with rapid-pacing induced CHF (Harker-Murray et al. 2000). In this study, serum or myocardial coenzyme Q10 concentrations were not reduced in dogs with CHF, nor did coenzyme Q10 supplementation increase myocardial concentrations or improve cardiac measurements [although serum concentrations did increase (Harker-Murray et al. 2000)]. The current recommended (but empirical) dose in dogs is 30–90 mg PO BID, depending upon the size of the dog. Controlled prospective studies

will be necessary to accurately judge the efficacy of this supplement.

GENERAL NUTRITIONAL ISSUES FOR DOGS AND CATS WITH CARDIAC DISEASE

No single diet is ideal for every animal with cardiac disease, and it is important to take each patient's individual characteristics into consideration. Animals may present for coughing, restless sleeping, exercise intolerance, or may be completely asymptomatic for cardiac disease. The nutritional modifications (and medications) selected will vary depending on the clinical signs exhibited. Physical examination findings also are important. An obese animal will requires a different caloric intake than one that has weight loss, while a dog with ascites or other signs of active congestion require greater sodium restriction than a dog that is asymptomatic. Diagnostic test results also help to determine the optimal nutrient modifications. For example, a biochemistry profile might demonstrate azotemia, hypo- or hyperkalemia, or hypoalbuminemia, all of which would affect diet selection. If thoracic radiographs show pulmonary edema or pleural effusion, more sodium restriction is indicated. Echocardiographic and electrocardiographic results also are important in designing the optimal medical and nutritional therapy. Concurrent diseases are very common in animals with cardiac disease (61% of dogs and 56% of cats) and may affect diet choice [e.g., a dog with gastrointestinal disease and CHF may require a different diet than one with CHF alone (Freeman, Rush et al. 2003; Torin et al. 2007)]. Finally, owner expectations and individual animal taste preferences will affect the diet that will be optimal for a given animal. All of these issues can help to determine the individual animal's nutrients of concern, and, based on these, one can select the optimal diet or diets.

Based on these patient parameters, one or more diets can be selected for the individual patient. Diets designed specifically for patients with cardiac disease can be selected. Some may include supplemental taurine, carnitine, arginine, antioxidants, or n-3 fatty acids. In some cases, a veterinary diet designed for another disease or an over-the-counter diet may have the properties desired for an individual patient. The authors generally try to offer a choice of diets so that the owner can determine which is most palatable to the pet. Having a number of choices is particularly beneficial for animals with severe CHF, in which a loss of appetite is common.

One of the keys to achieving optimal dietary intake is to be aware that sodium intake (or intake of any other nutrient, for that matter) comes from a number of sources: the pet food, treats, table food, and foods used to administer medications. Therefore, addressing each of these with the owner is important. Ninety-two percent of dogs and 33% of cats with cardiac disease receive daily treats or table food (Freeman, Rush et al. 2003; Torin et al. 2007). Treats and table food are often very high in sodium so this can be a significant source of sodium for some animals. Another significant source of sodium and other nutrients is the method used for medication administration. Fifty-seven percent of dogs with cardiac disease are administered their medications or dietary supplements in food, mostly high-sodium foods such as cheese, peanut butter, or deli meats (Freeman et al. 2003). The percentage of cats with cardiac disease whose medications are administered in foods is lower (34%) but can still be a significant source of sodium as the foods used were typically high sodium foods [e.g., cheese, baby food (Torin et al. 2007)]. Most owners are unaware of the sodium content of pet foods and table foods and need very specific instructions regarding appropriate pet foods, acceptable low-sodium treats, and methods for administering medications. Owners also should be counseled on specific foods to avoid.

All dietary changes should be done gradually over a period of 3 to 5 days. Diet changes should not be attempted in animals with acute CHF or in those with complications from medications (e.g., digoxin toxicity or azotemia due to overzealous diuretic use) as this may induce food aversions. In these patients, the goal should be to encourage food intake while avoiding high-sodium diets. Once a patient has been stabilized (usually at the time of the recheck visit 5 to 10 days later), a gradual change to the selected diet(s) can be instituted. It also is important to instruct the owner to notify the veterinarian if the patient does not eat adequate amounts of the new food so that other options can be devised.

While dogs and cats with cardiac disease can be a challenge to treat, they can be managed successfully when both medical and nutritional aspects of the case are addressed and when the treatment is individualized to the patient.

Nutrients of Concern to Consider in Cardiac Disease

- Calories
- Protein
- Fat
- Sodium
- Magnesium
- Potassium
- B vitamins

SUMMARY

- Cardiac disease is one of the most common diseases in dogs and cats and optimal nutrition may reduce the medication an animal requires, reduce complications, improve quality of life, and may slow the progression of the disease.
- No single diet is ideal for every animal with cardiac disease, and it is important to take each patient's individual characteristics into consideration.
- Concurrent diseases are very common in animals with cardiac disease, and nutritional modifications will vary depending on the clinical signs exhibited.
- Numerous other nutrients such as taurine, L-carnitine, arginine, coenzyme Q10, n-3 fatty acids, and antioxidants can have a role in managing cardiac disease. The use of some of these has more evidence than the use of others.
- Mild sodium restriction and the maintainenance of an optimal body condition are the two main goals in animals with asymptomatic cardiac disease.
- As cardiac disease progresses and congestive heart failure develops, many dogs begin to lose weight and develop cardiac cachexia. Managing dogs with cardiac cachexia can be challenging but is more successful when identified and addressed early in the process.
- It is important to recognize that sodium and other nutrient intake comes from a number of sources—the pet food, treats, table food, and foods used to administer medications. Obtaining a complete diet history will help the clinician develop dietary recommendations to meet each individual animal's needs.

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Nutritional Management of Oncological Diseases

19

Glenna E. Mauldin

Cancer is common in pet cats and dogs. Effective treatments including chemotherapy, radiotherapy, and surgery are available for many tumor types, and treated animals can enjoy prolonged survival with excellent quality of life. Nutrition always plays a central role in the successful and comprehensive management of cats and dogs with neoplastic disease. However, differences in tumor biology as well as wide individual variation in preexisting nutritional status mean that no single diet is appropriate for every animal with cancer. This chapter will first review what is known about the complex relationship between nutritional status and cancer in cats and dogs. Practical recommendations regarding selected nutritional requirements in the individual animal will then be discussed. Finally, a systematic method that can be used to evaluate novel nutritional claims for cats and dogs with cancer will be presented. The primary purpose of this chapter is to provide practical techniques that will assist the pet owner and the veterinarian in providing optimal, individualized nutrition for cats and dogs with malignant disease.

NUTRITIONAL STATUS IN CATS AND DOGS WITH CANCER

Weight Loss and Cachexia

Neoplastic disease is classically associated with weight loss. Severe weight loss in an individual with cancer is called "cancer cachexia," and this syndrome is characterized clinically by weight loss, fatigue, anemia, and loss of lean body mass and fat stores (Fearon et al. 2001; McKinlay 2004). Cancer cachexia is common in people, and its prevalence varies with tumor type (DeWys et al. 1980). While it occurs less frequently in people with relatively treatment-responsive tumors such as lymphoma, it is seen in over 80% of people with tumors of the stomach or pancreas. Regardless of the underlying tumor type, however, weight loss is clinically important because it has a negative effect on quality of life and prognosis (Fearon et al. 2001; Langer et al. 2001). Cancer cachexia causes weakness that compromises the ability to perform simple daily functions; it changes the pharmacokinetics and pharmacodynamics of chemotherapy drugs, increasing treatment-related toxicity and decreasing the patient's ability to tolerate aggressive treatment; and it is associated with shorter survival times and is a common immediate cause of death in people (Fearon et al. 2001; Holder 2003; Langer et al. 2001).

Cancer cachexia in cats, dogs, and people can be divided by underlying cause into two major categories: primary and secondary (Strasser and Bruera 2002). Secondary cancer cachexia is caused by any one of a variety of functional abnormalities that are not necessarily specific to neoplastic disease. For instance, tumors that involve the gastrointestinal tract can interfere physically with food intake, digestion, or absorption. Radiation and chemotherapy can also decrease nutrient utilization by changing taste and smell perception, by inducing nausea and vomiting, or by causing lethal injury to cells of the gastrointestinal epithelium. In contrast, primary cancer cachexia is an incompletely understood paraneoplastic syndrome that has been described in both people and animals with malignant disease. Unlike secondary cancer cachexia, it cannot be reversed through increased food

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intake or assisted feeding (Brennan 1977). This is because tumor-induced changes in metabolism force the inefficient use of energy through altered intermediary metabolism of fat, protein, and carbohydrate. This in turn leads to the depletion of lean body mass and fat stores that is characteristic of cancer cachexia. No matter what the quantity of nutrients fed or how they are provided, it is impossible to meet the patient's requirements (Fearon et al. 2001; Strasser and Bruera 2002).

Recent studies indicate that primary cancer cachexia is most likely caused by interrelated changes in numerous inflammatory mediators that have wide-ranging effects on energy and protein metabolism. Interleukin-1α (IL-1α), IL-1β, IL-6, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and various eicosanoids have all been implicated in this scenario, and they are believed to be ultimately responsible for producing the biochemical or metabolic abnormalities considered typical of primary cancer cachexia (McCarthy 2003; Tisdale 1999). Abnormalities that have been specifically documented in dogs with naturally occurring tumors have included increased serum lactate and insulin concentrations (Vail et al. 1990); increased serum lactate and insulin concentrations after an intravenous glucose tolerance test (Ogilvie, Walters et al. 1997); altered lipoprotein profiles (Ogilvie, Ford et al. 1994); and increased urinary nitrogen excretion and whole-body glucose flux with concurrently decreased whole-body protein synthetic rates (Mazzaferro et al. 2001). Such changes are associated with increased energy expenditure in the tumor-bearing host, which is hypothesized to be the fundamental reason for weight loss in primary cancer cachexia. However, while the predicted increase in energy expenditure can be documented among weight-losing cancer patients in some studies, it is normal or even decreased in others (Fearon et al. 2001; Ogilvie, Walters et al. 1993; Ogilvie, Walters et al. 1996; Strasser and Bruera 2002; Tisdale 1999). Further studies are needed to better define the relationship between energy expenditure and primary cancer cachexia.

Body Condition in Cats and Dogs With Cancer

The common occurrence of cancer cachexia and its negative impact on quality of life and survival is well accepted in people. However, even though some of the biochemical changes considered characteristic of primary cancer cachexia have been shown to be present in dogs with naturally occurring tumors, a specific and significant association between these changes, the presence of primary cancer cachexia, and clinical outcome is not well documented in animals. Some authors have maintained that if characteristic metabolic changes are present they must inevitably lead to weight loss and primary cancer cachexia, but evaluation of the literature suggests that this may not always be the case. For instance, in one study conducted in dogs treated at a referral oncology practice, only 4% of cases were cachectic based on body condition score, while 29% were obese; 15% of the dogs had clinically significant muscle wasting. Weight loss was documented in 68% of dogs, but it represented less than 5% of the precancer body weight in 31% of cases. The overall conclusion of this study was that weight loss was less common and less severe in dogs with neoplastic disease than in people (Michel et al. 2004). The distribution of body condition scores among dogs with a variety of types of cancer was also investigated and compared to dogs without cancer in a much larger study (Weeth et al. 2007). These authors found that dogs with malignant tumors were somewhat less likely to be overweight compared to dogs without neoplastic disease, but there was no difference in the prevalence of underweight or very thin dogs between the two groups. This study also showed that age, breed, neuter status, tumor type, and a history of corticosteroid administration are important confounding factors that affect nutritional status among dogs with cancer as well. Interestingly, there was no difference in historical body weight and body weight at the time of initial evaluation in a subgroup of 57 dogs in this study that had B-cell lymphoma. In addition, the body condition score distribution of these dogs did not differ from that of the noncancer controls. While previous work has demonstrated that multiple biochemical changes typical of primary cancer cachexia specifically occur among dogs with lymphoma, the results of this study indicate that they do not often lead to weight loss.

Fewer data that evaluate nutritional status in cats with cancer are available. One study has examined body condition score and its effect on prognosis in cats with neoplastic disease (Baez et al. 2007). These investigators found that unlike the dog, almost half of the cats they evaluated were underweight or very thin, and over 90% of them had evidence of muscle wasting (see Fig. 19.1). Their data also showed that body condition score was strongly correlated with survival time and prognosis: Cats with decreased body condition scores had markedly shorter survival times. However, no control animals were included in this study. Preliminary data suggest that sick cats are more likely to experience a decline in nutritional status than sick dogs, regardless of whether they have cancer or not (Daniel et al. 1999). Further work is needed to determine if the relatively lower body condition scores observed in the cats

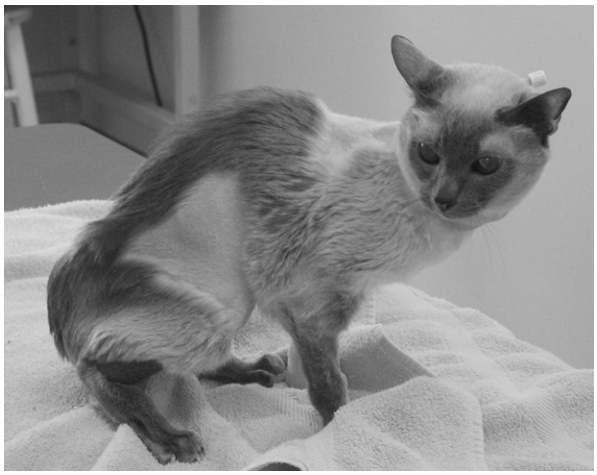

Fig. 19.1. A cat with gastrointestinal lymphoma and an esophagostomy tube for assisted enteral feeding. Cats with cancer are likely to have weight loss, which has a negative impact on prognosis.

in this study were specifically related to the presence of underlying neoplastic disease, or whether they represent a more generic feline response to illness.

While much of the focus in cats and dogs has been on defining the relationships between body condition score and neoplastic disease at the time of a cancer diagnosis, several authors have also searched for a potential role for body condition over time in the pathogenesis of cancer in the dog. Dogs with mammary gland tumors have been most frequently studied. One case control study investigated the effect of body condition and diet on the risk of mammary cancer in dogs, and found that risk was decreased in both spayed and unspayed dogs that had been thin at 9 to 12 months of age (Sonnenschein et al. 1991). A similar study found that obesity at 12 months of age was associated with an increased risk of mammary cancer. This study also implicated regular consumption of human foods in tumor development, because dogs with breast cancer were more likely to have high intake of red meat (Alenza et al. 1998). The authors of a third study were unable to find an association between survival and obesity in dogs with malignant mammary tumors, although they did not specifically evaluate the impact of historical obesity on tumor development later in life (Philibert et al. 2003). Overall, these studies suggest a possible role for fat intake and obesity in the pathogenesis of canine mammary tumors, as is the case in women. More work is needed to better define this relationship.

NUTRITIONAL MANAGEMENT OF CATS AND DOGS WITH CANCER

Energy

The target food intake for a cat or dog with cancer is dictated by the animal's energy requirements. A complete and balanced ration is the most convenient way to provide nutrition because except for water, basic requirements for all essential nutrients, including vitamins and minerals, are met when the quantity of food necessary to meet daily caloric needs is consumed. A food that has passed AAFCO (Association of American Feed Control Officials) feeding trial testing is preferred. Regardless of the ration chosen, water intake and fluid balance must be monitored carefully; supplements to correct specific nutrient deficiencies (i.e., potassium, phosphorus, vitamin K) are occasionally indicated.

Many different equations have been used to estimate maintenance energy requirements (MERs) in healthy cats and dogs, but there is no consensus regarding which one is most accurate (see Chapter 3). Furthermore, the effect of underlying neoplastic disease on MERs in small animals is unknown, and altered energy expenditure is certainly possible in affected animals. Despite these factors, however, calculation of MERs remains the most practical way to estimate individual energy requirements for a self-supportive and weight-stable cat or dog with cancer. Serial nutritional assessments are then used to decide whether adjustments in food intake are needed to maintain optimal body condition. The energy needs of hospitalized animals with cancer are similarly incompletely defined. Typically, the resting energy requirement (RER) is used as an approximation of the calories needed by a critically ill small animal (see Chapter 3) (Remillard, Armstrong et al. 2000). Some authors also multiply the RER by an illness factor, which is intended to individualize energy intake based on the severity of underlying disease: Requirements are believed to be higher in people and animals with more critical illnesses (Bartges 1996; Richardson and Davidson 2003). In general, however, conservative illness factors (between 1.0 and 1.4) are safest because they are less likely to lead to the metabolic complications that can result from overfeeding. Once again, the animal's clinical response to the initial level of intake should be carefully monitored through repeated nutritional assessment so that adjustments to food intake can be made as indicated.

As already discussed, many cats and dogs with neoplastic disease are overweight and the nutritional management of these animals can be a challenge (see Fig. 19.2). The health risks of obesity in otherwise normal small animals are well established and include musculoskeletal disease,

Fig. 19.2. A dog with metastatic neoplastic disease. Many dogs with cancer are overweight or obese.

glucose intolerance, diabetes mellitus and immunosuppression (Burkholder and Toll 2000). Dogs that are maintained in optimal body condition have also been shown to live longer than dogs that are overweight (Lawler et al. 2005). These facts suggest that weight loss would also be beneficial in obese cats and dogs with neoplastic disease, although this is probably true only for animals whose expected survival times are long enough to justify the time and effort necessary to achieve leaner body condition. Regardless, the weight reduction protocols that are routinely used in otherwise healthy animals are not necessarily suitable in all animals with cancer. A conservative reduction in caloric intake below the calculated MER at ideal body weight is probably most appropriate for overweight cats and dogs that are clinically stable and self-supportive: The goal is to gradually achieve an ideal body condition score and optimal nutritional status. Aggressive weight loss programs are contraindicated during critical illness, even in cats and dogs that are very obese. Severe caloric restriction in a sick animal could contribute to clinically significant protein-calorie malnutrition, with hypoproteinemia, loss of lean body mass, delayed wound healing, immunosuppression, and compromised organ function. Stabilization of the animal's medical condition is the first priority, and weight reduction should be postponed until this has been achieved. The specific steps involved in designing a successful weight loss program for an obese cat or dog are discussed in Chapter 9 and have been previously described (Burkholder and Toll 2000).

Voluntary intake is the most practical and efficient way to meet the energy needs of cats and dogs with cancer. However, for this approach to be successful the animal's caloric requirement must actually be calculated and the daily quantity of food consumed must be measured as accurately as possible, at least initially. If there is a consistent discrepancy between the amount of food needed to meet requirements and the amount that is actually being eaten, then assisted feeding is indicated. There are three basic techniques for assisted feeding, and they can be used singly or in combination: pharmacologic appetite stimulation, assisted enteral feeding, and assisted parenteral feeding. Pharmacologic appetite stimulation can be convenient and cost effective, but it is essential to confirm drug efficacy through careful measurement of actual food intake. Failure to take this step can result in a prolonged delay in the initiation of more appropriate and effective methods of assisted feeding (Baron 2000). Furthermore, while the appetite stimulants used most commonly in cats and dogs with cancer are probably diazepam and cyproheptadine, there are no clinical studies that provide convincing and objective evidence of efficacy for either one. Megestrol acetate is used more often in people with cancer (McQuellon et al. 2002), but once again there are no controlled trials that confirm the benefit of this drug in anorexic cats or dogs with neoplastic disease. More work is needed to define the role of appetite stimulants in the management of cats and dogs with cancer.

For a cat or dog with cancer that is not able to meet its energy requirements through voluntary intake, assisted feeding can be provided enterally or parenterally. Enteral or tube feeding is almost always preferred because it maintains gut health and function and allows nutrients to be metabolized through normal pathways (Cohen and Lefor 2001; Mercadante 1998). Enteral support is usually cheaper and easier to administer than parenteral nutrition and is associated with fewer potential complications. An additional specific advantage of enteral feeding for cats and dogs with cancer is that there is some evidence that parenteral feeding stimulates the progression of neoplastic disease in people and rodent models (Mercadante 1998; Torosian and Donoway, 1991). Indwelling tubes that can be used to deliver enteral support in cats and dogs with cancer include nasoesophageal, pharyngostomy, esophagostomy, gastrostomy, and enterostomy tubes. The indications, surgical techniques for placement and use of these tubes are discussed in Chapter 20 and are also described in detail elsewhere (Mauldin and Davidson 2003).

Assisted parenteral feeding is sometimes indicated in cats, dogs, and people with cancer. It is the only option available when the gastrointestinal tract is completely nonfunctional. It can also be used to help treat inflammatory

intestinal conditions because it permits complete bowel rest. Parenteral feeding may be considered as well in selected cases where hemodynamic instability or coagulopathy would make general anesthesia for surgical placement of a feeding tube too risky (Mauldin and Davidson 2003). Despite these apparent indications and advantages, however, a number of studies suggest that parenteral feeding actually has a negative impact on outcome when it is used in people with neoplastic disease. People with cancer who receive parenteral nutrition have more complications, marginal improvement in nutritional status, and trends toward decreased survival (Fearon et al. 2001; Mercadante 1998). It seems likely that this is related at least in part to the compromised gut function that can occur during parenteral feeding. Lack of ingesta within the intestinal tract leads to intestinal mucosal atrophy, compromised gut immunity, and increased rates of bacterial translocation (Alverdy et al. 1985; Mercadante 1998; Remillard, Guerino et al. 1998). A combination of parenteral nutrition and enteral support should always be considered for animals that will tolerate it: Even very small amounts of food within the intestinal tract help to prevent deterioration in function. The techniques involved in assisted parenteral feeding are discussed in detail in Chapter 21 and elsewhere (Mauldin and Davidson 2003).

Initiation of assisted enteral or parenteral feeding is necessary and lifesaving for many cats and dogs with malignant disease. It improves ability to tolerate aggressive antineoplastic therapy and speeds recovery from critical illness. However, the indications for nutritional support and the individual animal's long-term prognosis should both be carefully considered before assisted feeding is implemented. Nutritional support does not improve nutritional or functional status in people with cancer who have a very short life expectancy (Angus and Burakoff 2003), and the same is likely to be true in cats and dogs with terminal disease. When all treatment options have been exhausted, and there is no reasonable probability of restoring an acceptable quality of life, nutritional support may only serve to prolong an uncomfortable death. The pet owner must obviously be involved in deciding whether or not to use assisted feeding techniques in their animal, but it is important for the clinician to be very clear and realistic about what can actually be achieved. Assisted feeding should provide tangible benefit to every patient that receives it (McKinlay 2004).

Calorie Sources

A change in diet is not automatically indicated in every cat or dog with cancer. Each animal must be carefully and individually evaluated, and those that are already maintaining good body condition on a high-quality complete and balanced food that is well tolerated and accepted may remain on this ration until there is an objective reason to change. In cases where a diet change is being considered, several factors are used to decide which ration is best for a particular animal, but distribution of calories between protein, fat, and carbohydrate is one of the most important. Optimal caloric distribution is determined by the results of nutritional assessment, the type of cancer being treated, and the presence and severity of concurrent diseases. Since these factors vary from animal to animal, it is not possible to recommend a single ration or even ration type that will provide optimal nutrition in all cases. Instead, every animal should undergo a thorough and standardized nutritional assessment. Dietary recommendations are made only after this process is complete.

The commercial rations typically recommended for cats and dogs with neoplastic disease and normal liver and kidney function deliver 30% to 35% of calories as protein, contain as few carbohydrate calories as possible, and are high in fat. The commercial rations most likely to fit this profile are prescription critical care products, performance rations, and puppy or kitten foods. A prescription product intended specifically for dogs with cancer (n/d®, Hills Pet Nutrition Inc., Topeka, KS) is also available; this product is high in fat and protein content and is enriched with n-3 fatty acids. The high protein content of all these products helps to preserve lean body mass and prevent the deleterious effects of protein-calorie malnutrition. Their high-fat and low-carbohydrate content has several potential advantages. Theoretically, this takes advantage of the metabolic differences between tumor and normal host cells. Since neoplastic cells do not possess the biochemical pathways needed to oxidize fat, a high-fat low-carbohydrate diet should preferentially supply energy to host tissues while avoiding inadvertent "feeding" of the tumor. Although a high-fat ration normalized carbohydrate metabolism and prolonged survival times in a subset of dogs with lymphoma in one study, more work is needed to confirm this finding (Ogilvie, Fettman et al. 2000). Fat also provides more calories per gram (8.5 kcal/g) than protein (3.5 kcal/g) or carbohydrate (3.5 kcal/g). The increased energy density of a high-fat ration is helpful when voluntary food intake is decreased, and during tube feeding as well. Finally, high-fat rations are more palatable, which may improve food intake in some animals. Most cats and dogs can tolerate up to 65% of their total energy requirement as fat, as long as they are permitted a period of adaptation (Remillard, Armstrong et al. 2000).

Despite these potential advantages, it is important to recognize that a high-fat, high-protein diet is contraindicated in some cats and dogs with cancer. Animals with a history of dietary fat intolerance should continue to have their dietary fat intake restricted whether they have underlying neoplastic disease or not. High-fat diets also make it more difficult to maintain optimal body condition in the substantial proportion of animals with cancer that are overweight or obese rather than losing weight. Switching to a high-protein diet for a cat or dog with cancer that also has concurrent and significant renal or hepatic insufficiency may precipitate clinical decompensation that is difficult to reverse. Carbohydrate calories can be substituted in any of these situations where protein or fat intake must be restricted, although it makes sense to use complex rather than simple sugars to the greatest degree possible in order to avoid sharp spikes in blood glucose concentration. Regardless of their effect on tumor cells, carbohydrates may not be used efficiently by tumor-bearing animals because of insulin resistance and glucose intolerance (Ogilvie, Walters et al. 1997).

Once the optimal distribution of calories for an individual cat or dog with cancer has been identified, the commercial rations that meet these criteria are identified. Complete and balanced products that have been AAFCO feeding trial tested are preferred. A final selection is made after considering factors such as digestibility, fiber content, palatability, necessity for tube feeding, cost, and owner convenience. Historical episodes of food intolerance as well as strong preferences by the animal for certain diet formulations (dry, canned, or semi-moist) or flavors should also be taken into account (see Fig.19.3).

Protein and Amino Acids

As already discussed, a generous protein intake is usually recommended for cats and dogs with cancer. The goal is to support anabolic processes to the greatest degree possible, and in so doing prevent protein-calorie malnutrition. However, providing dietary protein at levels above the animal's needs is expensive and provides little benefit. Protein requirements are dictated by requirements for essential amino acids that cannot be synthesized endogenously. Many studies in numerous species indicate that these requirements are increased during critical illness regardless of etiology (Bartges 1996; Richardson and Davidson 2003), and it is essential that sufficient protein be provided to meet them. Since it is difficult to determine exactly what the protein requirements are of an individual cat or dog with cancer, the most practical approach is to supply protein at a level that meets all anticipated needs and also incorporates an additional generous increment that will meet any unrecognized requirements. As described previously, providing protein at 30% to 35% of total calories will achieve this goal in most animals; repeated nutritional assessment should still be used to reevaluate patient response and make any needed adjustments. However, once anabolic pathways (i.e., hepatic albumin synthesis) are operating at maximal capacity, it is not possible to force increased rates of activity by feeding ever higher quantities of protein. Amino acids supplied in excess of known plus unknown requirements will either be directly oxidized as an unnecessarily expensive source of energy, or deaminated and metabolized to glucose. Azotemia results in some cases. If both amino acid and total energy requirements of the animal are exceeded, then unneeded amino acids will eventually be stored as fat. None of these scenarios is desirable in a cat or dog with cancer.

Individual amino acids such as glutamine and arginine are often alleged to provide particular benefit for animals and people with neoplastic disease. Supplementation may be recommended, although the most appropriate doses and methods of administration in cats and dogs with cancer are largely unknown. Glutamine is the most abundant free amino acid in both plasma and intracellular pools. Although it is strictly defined as a nonessential amino acid, it plays an important role in many metabolic pathways and is "conditionally essential" during critical illness. Glutamine has two nitrogen groups, which allows it to function as a major means of nitrogen transport between tissues (Smith 1990). It is a primary substrate for ammonia synthesis in the kidney, and also participates in the synthesis of nucleotides and many other macromolecules. Glutamine serves as a critical energy substrate for enterocytes, and it is also required by lymphocytes and other rapidly dividing cell populations (Smith 1990). Substantial decreases in plasma and free intracellular glutamine concentrations occur in skeletal muscle in critically ill people: Intracellular glutamine represents a vital storage pool of carbon and nitrogen that can be mobilized to quickly meet the needs of many tissues (Rennie et al. 1989; Smith 1990). A high intake of glutamine helps prevent subsequent loss of lean body mass by supporting muscle protein synthesis and decreasing muscle protein catabolism (Hammarqvist et al. 1990, Yoshida et al. 2001). Even more important is the central role played by glutamine in maintaining normal gastrointestinal and immune system function during illness (Remillard, Guerino et al. 1998; Souba, Klimberg, Plumley et al. 1990). Glutamine has also been suggested to accelerate healing of acute radiotherapy side effects involving the oral mucosa in dogs (Khanna et al. 1995), and to protect

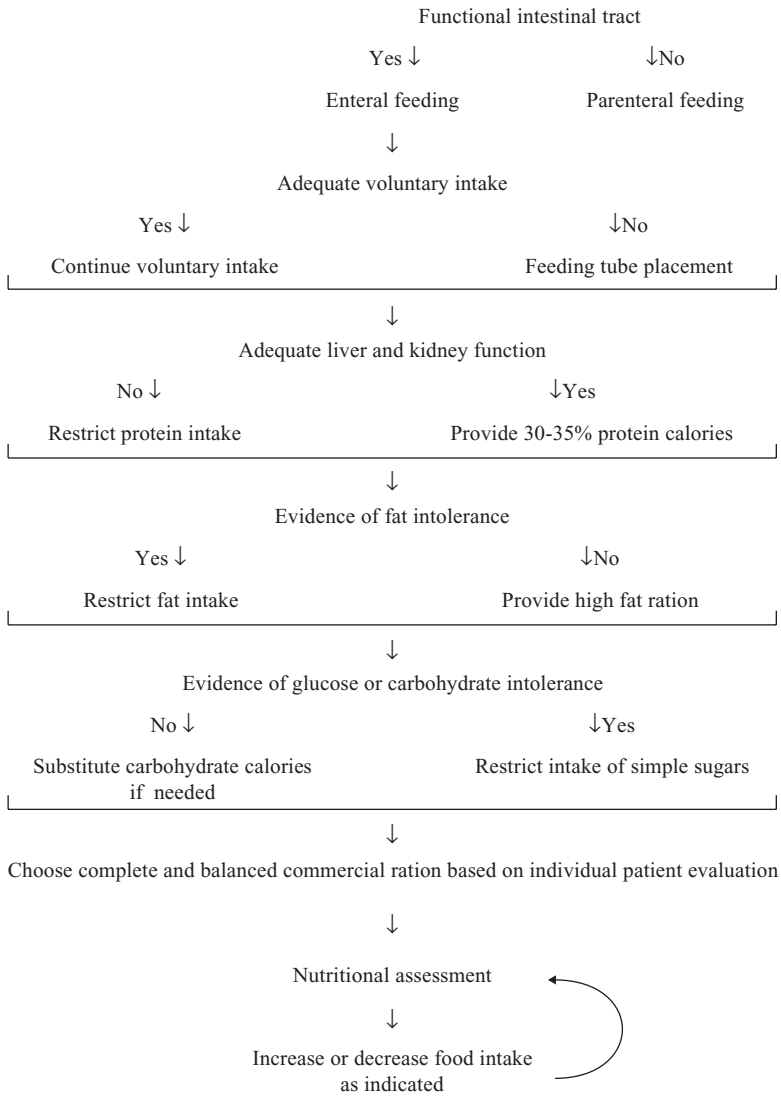

Fig. 19.3. Flowchart outlining the clinical decision-making process involved in making a diet change for a cat or dog with cancer.

gut immunity and integrity in individuals receiving radiotherapy or chemotherapy (Nitenberg and Raynard 2000; Yoshida et al. 2001). Accordingly, the prescription critical care rations often recommended for cats and dogs with cancer are typically supplemented with glutamine. Further study is needed to more precisely define the role of glutamine supplementation for cats and dogs with cancer.

Arginine is an essential amino acid in cats and dogs. It has a number of functions that are potentially important in both people and animals with cancer: it plays a central role in urea and collagen synthesis; it participates in the release of insulin, growth hormone, and insulin-like growth factor-1; it modulates immune function; and it supports wound healing (Nitenberg and Raynard 2000). Supplementation with arginine increases collagen synthesis and augments wound breaking strength (Chyun and Griminger 1984). Lymphocytes have an absolute requirement for arginine, and higher intakes increase lymphocyte mitogenic response, improve T-cell function, and have been shown to enhance *in vitro* and *in vivo* antitumor cytotoxicity

(Daly et al. 1998; Moskovitz and Kim 2004). Critically ill people that receive arginine supplementation have decreased incidence of postoperative wound infection, and shorter hospital stays (Caparros et al. 2001; Daly et al. 1992; Moskovitz and Kim 2004). While the specific benefits of added arginine in cats and dogs with cancer are largely unknown, similar benefits are certainly possible, and several commercial critical care rations for small animals are enriched with arginine. However, further work is needed to document the specific advantages that may exist.

Omega-3 (n-3) Fatty Acids

Prescription pet foods intended for use in cats and dogs with cancer are typically enriched with n-3 fatty acids, and additional supplementation above the level supplied in the diet is often recommended as well. Although the appropriate doses, methods of administration, and indications for n-3 fatty acids are not completely defined, their use is supported by relatively convincing objective evidence, at least in dogs and people. Marine oils are especially rich in the desired long-chain n-3 fatty acids, and because of this they are the preferred dietary source for cats and dogs because these animals are unable to efficiently convert the shorter chain n-3 fatty acids contained in vegetable oils such as flax. Changing the dietary ratio of n-6 to n-3 fatty acids alters the fatty acid composition of cell membranes throughout the body, and this in turn impacts cell membrane eicosanoid production, cytokine synthesis, and the inflammatory cascade. Specifically, series 4 leukotrienes and series 2 prostaglandins are derived from the n-6 fatty acid arachidonic acid and are pro-inflammatory, while series 5 leukotrienes and series 3 prostaglandins are synthesized from the long-chain n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and are less potent stimulators of inflammation. Studies have confirmed that the eicosanoids produced during inflammation in the dog vary with the dietary n-6 to n-3 fatty acid ratios, and that the inflammatory response can be attenuated by n-3 fatty acid supplementation in conditions such as atopy (Scott et al. 1997; Vaughn et al., 1994).

Ultimately, n-3 fatty acid interaction with eicosanoid production most likely affects the inflammatory response by altering synthesis of cytokines such as IL-1, TNF-α, and IL-6 (LeBlanc, Horohov et al. 2008). It is therefore reasonable to hypothesize that an inflammatory condition such as primary cancer cachexia might be ameliorated through n-3 fatty acid supplementation. Added n-3 fatty acids have in fact been demonstrated to decrease synthesis of pro-inflammatory cytokines and stabilize body condition in people with pancreatic cancer (Barber et al. 2001; Fearon et al. 2001); they have also been shown to help reverse weight loss in mice bearing implanted tumors (Beck et al. 1991). In another study, people with advanced neoplastic disease who received n-3 fatty acid supplements had improved immune function and prolonged survival compared to unsupplemented controls (Gogos et al. 1998). Finally, although they did not have concurrent weight loss, some abnormalities in carbohydrate metabolism resolved in dogs with lymphoma that were fed a test diet enriched with both n-3 fatty acids and arginine (Ogilvie, Fettman et al. 2000).

Despite these potential benefits, there are multiple risks associated with excessive intake of n-3 fatty acids in people and animals. Increased intake of n-3 fatty acids causes decreased synthesis of thromboxane A_2 and increased production of prostaglandin I_3 in people, leading to decreased platelet aggregation and vasoconstriction (Kristensen et al. 1989). While this effect might inhibit metastasis and has been suggested as the reason for the decreased incidence of atherosclerotic disease observed among fish-eating Inuit peoples, it could also predispose some individuals to hemorrhage. Although studies have thus far been unable to demonstrate this to be a clinically significant problem in the dog (Boudreaux et al. 1997; McNeil et al. 1999), decreased platelet function has been reported in cats fed a ration enriched with n-3 fatty acids (Saker et al. 1998). Consumption of diets containing high levels of n-3 fatty acids may also compromise normal immune function. Decreased lymphocyte proliferation has been documented in people and dogs (LeBlanc, Dietrich et al. 2007; Meydani et al. 1991), and suppression of cell-mediated immunity has been observed in n-3 fatty acid supplemented dogs (Wander et al. 1997). Increased tissue membrane lipid peroxidation caused by the ingestion of large quantities of polyunsaturated fatty acids has been suggested as the factor responsible for these alterations in immune function. Some authors have also speculated that relative vitamin E deficiency in the face of n-3 fatty acid supplementation may play a role (Meydani et al. 1991; Wander et al. 1997), although at least one investigator was unable to confirm this in dogs (LeBlanc, Horohov et al. 2008). Finally, n-3 fatty acids have been implicated as potential inhibitors of wound healing. However, histologic evidence of such an effect could not be demonstrated in the dog (Mooney et al. 1998).

Antioxidants

People who eat large quantities of fruits and vegetables have a significantly decreased risk of certain types of

cancers such as carcinomas of the lung, head and neck, and upper gastrointestinal tract (Johnson 2004; Llewellyn et al. 2004; Rao et al. 1994). Nutrients that could be responsible for this protective effect include antioxidants such as beta carotene; lutein; selenium; and vitamins A, C, and E (Mandelker 2008a). These nutrients, among others, are added to many commercial pet foods and may also be recommended for additional supplementation beyond what is present in the diet. Marketing often suggests to the consumer that the added antioxidants will help prevent cancer in animals that consume these products.

There are three potential scenarios in which antioxidant supplementation could be considered for the cat or dog with cancer. First, antioxidants could be administered over a period of years as a cancer preventative. Chronic oxidative stress with formation of reactive oxygen species is hypothesized to be one of the basic mechanisms causing cancer (Mandelker 2008b). Oxidative injury causes DNA damage and eventually this can lead to malignant transformation with establishment of a neoplastic cell population. This process is more likely to occur when antioxidant capacity is marginal or inadequate, so appropriate supplementation could theoretically prevent it. Preliminary work in dogs with mammary tumors showed that the degree of lipid peroxidation was greater in tumor tissue compared to adjacent normal tissues, suggesting at least the possibility of a role for oxidative damage in the development of these lesions. However, increased antioxidant activity was found within the tumors assayed as well, calling into question whether increased intake of antioxidants in these animals could have had any protective effect at all (Kumaraguruparan et al. 2005). In another study, supplementation with selenium appeared to decrease DNA damage and prevent possible progression to tumor by promoting programmed cell death in non-neoplastic prostatic epithelial cells in geriatric laboratory beagles (Waters et al. 2003). However, very few, if any, objective data are available that actually assess the potential antineoplastic effect of long-term dietary antioxidant supplementation in pet cats and dogs. Which antioxidants might be most effective, at what dietary concentration or dose, and over what period is unknown. Various antioxidant cocktails that could play a role in preventing cancer are often advertized as one of the benefits of rations intended for use in "senior" pets, but given the hypothesized mechanism of this protective effect a legitimate question is whether the age of 7 or 8 (the age at which senior diets are typically recommended) might be too late for intervention. If oxidative stress with the potential to eventually induce malignant transformation is present over the lifetime of the animal, then antioxidant supplementation might be even more beneficial if it is provided over the same period. The studies that would be needed to answer these questions are probably prohibitively complex and costly: Large groups of cats and dogs would have to be fed standardized diets containing different concentrations of various antioxidants beginning at different ages, so that potential differences in the incidence of neoplastic disease depending on the type and duration of antioxidant supplementation could be documented.

A second situation in which antioxidant supplementation may be considered is during cancer treatment, with the primary intention of reducing the severity of some of the side effects of therapy. This is an area of considerable controversy in human oncology. Both chemotherapy and radiation therapy injure and kill cells through oxidative damage and generation of free radicals. The difficulty is that while this is a desired effect with respect to targeted cancer cells, the same process often leads to serious side effects when it occurs in normal host tissues. Many mainstream human cancer treatment centers currently advise individuals undergoing therapy to avoid taking high doses of any antioxidants, in order to maximize the efficacy of their cancer treatment (see the Memorial Sloan-Kettering Cancer Center website page "About Herbs, Botanicals, and Other Products"; http://www.mskcc.org/mskcc/html/11570.cfm). However, other authors disagree and use the contradictory results of published studies in this area to support their point of view (Simone et al. 2007). More well-designed, prospective studies are needed to resolve these questions in people; not surprisingly, no such studies exist for cats and dogs undergoing chemotherapy or radiotherapy. Until more specific information becomes available, the best recommendation is probably the same for cats and dogs as it is in people: High-level antioxidant supplementation should be avoided during cancer treatment.

A final situation where antioxidants could play a role is in prevention of tumor recurrence after completion of anticancer therapy. This has recently been examined in several large studies and meta-analyses in people. Unfortunately, the results have often been disappointing. First of all, it is not clear that taking antioxidants as supplements provides the same benefits as consumption of the same vitamins and minerals in their naturally occurring forms in whole foods (Johnson 2004). Furthermore, significantly increased rates of primary tumor recurrence or second primary cancers have actually been observed during supplementation with beta-carotene or vitamin E (Bairati et al. 2005; Omenn et al. 1996). While there can be no doubt that there are numerous, clear benefits associated with adequate

antioxidant intake in cats, dogs, and people, whether they have underlying cancer or not, more work remains to be done before antioxidant supplementation can be confidently recommended for tumor chemoprevention or management of cancer therapy side effects in any of these species.

NUTRITIONAL FADS

Supplements and Nutraceuticals

The owners of cats and dogs with cancer should always be asked very specifically about medications and nutritional supplements they are using. Dedicated pet owners frequently make significant changes to their feeding practices and may also add a wide variety of supplements and nutraceuticals to their animal's diet after a diagnosis of cancer has been made. Their goal is simply to take advantage of every possible intervention that may benefit their pet, but these changes and additions are made without veterinary advice in many cases. Some owners view veterinarians as poor sources of unbiased nutritional information, so do not feel there is any point in even starting a discussion on the subject. More often, however, owners just want to avoid the disapproval that they feel is likely to follow their admission that they are using alternative or complementary therapies in their pet. In order to provide the best recommendation for each individual animal, it is absolutely essential that the veterinarian remain objective, well-informed and nonjudgmental, and willing to engage in discussion.

A systematic approach to the evaluation of nutritional supplements, nutraceuticals, and novel feeding practices is the best way to ensure that the most appropriate advice is always given. Three basic questions must be answered in every case: (1) Does the product or practice work? (2) Is it safe? (3) Is the product or products being used of acceptable quality?

To answer the first question, a logical scientific hypothesis supporting the benefit of the supplement or practice in question should be clearly apparent. This should include knowing specifically what the active compounds or advantageous qualities of a particular product are, as well as access to studies published in the peer-reviewed scientific literature that describe the objective and consistent beneficial effects in controlled clinical trials. Ideally, these studies should be performed in cats and dogs with cancer; this is particularly true in the cat because of its numerous metabolic and nutritional peculiarities. However, data collected in human trials may also be helpful.

To answer the second question, reliable information from controlled studies investigating both the short- and long-term safety of the product in cats and dogs (or at least people) should be available. It is particularly important in animals with cancer to consider any possible interactions and contraindications with anticancer therapy in this regard.

Finally, to answer the third question there should be some means of objective assurance that the specific product or products being used is of good quality: this includes consistent concentration and availability of the active ingredients, as well as lack of contamination. A particularly valuable source of objective information that can be used throughout this three-step process is the "About Herbs, Botanicals, and Other Products" section of the Memorial Sloan Kettering Cancer Center website (http://www.mskcc.org/mskcc/html/11570.cfm). This site is constantly updated and provides citations for further reading where they are available. It is also separated into areas for health-care professionals and patients, and so it can be confidently recommended to pet owners as a source of reliable and readily understandable information.

Raw Foods

The feeding of raw foods to cats and especially dogs is increasingly popular. These diets are intended to mimic the diet of wild cats and dogs and are believed by their proponents to provide nutrition that is superior to traditional cooked pet foods. Proposed benefits of raw food diets include improved nutrient digestibility and absorption, increased health of coat and skin, decreased incidence of obesity and improved lean body mass, improved immune function, resolution of various degenerative diseases, and increased life span. Detractors point to the increased likelihood of nutritional imbalance, increased incidence of gastrointestinal foreign bodies because of the ingestion of bones, and the potential contamination of the diet with pathogens that may cause disease in both the pet and its owner. While controlled, long-term studies that objectively compare the advantages and disadvantages of the two approaches and definitively prove that one is better than the other do not yet exist, raw foods do pose one very significant concern for cats and dogs with cancer. Several studies show that raw pet foods and the ingredients used to prepare them can be contaminated with pathogenic bacteria including *Salmonella* spp. (Joffe and Schlesinger 2002). Cats and dogs with cancer can be significantly immunosuppressed, both by their disease and by its treatment, making life-threatening infections a legitimate risk when raw foods are used. For this reason, the owners of cats and dogs undergoing cancer treatment should be specifically counseled not to feed raw foods.

SUMMARY

- Severe weight loss in an individual with cancer is called "cancer cachexia."
- Weight loss decreases prognosis in cancer patients.
- Individualized nutritional assessment is essential for all cats and dogs with cancer.
  - Dogs are often overweight or obese.
  - Cats are more likely to have weight loss.
- Optimal food intake is dictated by energy requirements.
- Complete and balanced commercial pet foods that are relatively high in fat, low in carbohydrates, and provide ample protein are often used in cats and dogs with cancer.
- Dietary changes are not indicated in all cases.
  - Many animals can safely remain on their regular diet.
  - High-protein, high-fat diets are contraindicated in some animals with neoplastic disease.
- Sufficient evidence exists to recommend supplementing dogs (not cats) that have cancer with long-chain n-3 fatty acids, but the optimal dose and method of administration is unknown.
- Antioxidant supplements should not be administered to cats and dogs undergoing chemotherapy or radiation therapy.
- All supplements and novel nutritional therapies should be objectively and systematically evaluated before they are recommended for use in cats and dogs with cancer.

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Enteral Nutrition and Tube Feeding

20

Jennifer A. Larsen

Preventing or reversing malnutrition in hospitalized patients or those with chronic debilitating disease should be an important goal of all clinicians. In human medicine, it is known that malnutrition is associated with increased mortality and longer hospital stays, and this is a common problem in the elderly and chronically ill (Stratton and Elia 2006). While providing nutritional support by either parenteral or enteral routes has been beneficial, it is becoming apparent that utilizing the gastrointestinal tract whenever possible is important.

THE CASE FOR ENTERAL FEEDING

Although the human medical literature includes studies that fail to show a benefit of enteral over parenteral nutrition in critical illness (Reynolds et al. 1997; Eckerwall et al. 2006), there are also studies that show improvements in several important parameters, including indices of inflammation, intestinal permeability, and rates of complications (Windsor et al. 1998; Braga et al. 2002; Gupta et al. 2003; Louie et al. 2005). Also, a recent report demonstrated that enteral feeding in people with severe burns maintained and preserved intestinal health, including normal barrier function, motility, and blood flow (Chen, Wang et al. 2007). However, even studies that fail to show a benefit of enteral feeding over parenteral feeding do not demonstrate any negative effects and only reveal no differences between treatments. Recent literature reviews have analyzed the evidence from these comparative studies and have found that enteral feeding is more cost effective and results in overall significant decreases in complications with more positive outcomes (Gramlich et al. 2004; McClave, Chang et al. 2006; Jeejeebhoy 2007). In the veterinary literature, it has been shown in dogs with induced pancreatitis that parenteral nutrition (compared to enteral nutrition) has a negative impact on gut barrier function and is associated with decreased intestinal villus height, mucosal thickness, and total protein and DNA content, and that this occurs within just 7 days (Qin et al. 2002). It seems clear that the provision of adequate nutrition, administered enterally where possible, can be a powerful tool in the management of patients with a wide variety of disease conditions.

NUTRITIONAL SUPPORT OF VETERINARY PATIENTS

Many articles have described techniques for successfully providing enteral nutrition in veterinary patients (Abood and Buffington 1991; Bright 1993; Marks 1998; Waddell and Michel 1998; Daye et al. 1999; Stevenson et al. 2000; von Werthern and Wess 2001). Despite these resources, one study found that negative energy balance was very common in a population of hospitalized dogs (Remillard, Darden et al. 2001). This study also reported a significant and positive correlation between caloric intake and outcome. Reasons for failure to provide adequate nutritional support included inadequate feeding orders by the clinician, orders to withhold food, and patient's refusal to eat. There is evidence that animals with diseases that have been traditionally managed with "nil per os" (NPO) orders may actually benefit from early enteral feeding (Qin et al. 2002; Mohr et al. 2003). Additionally, solving problems that involve poor order writing and encouraging patient

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management that is inclusive of nutritional needs is perhaps simpler than overcoming a patient's anorexia.

There are different ways to accomplish enteral feeding, including voluntary intake. If an animal will eat adequate amounts of an appropriate diet for any disease states that may be present, intervention is not necessary. Voluntary intake can be encouraged with the utilization of various measures of altering diet palatability as well as managing the hospital environment (Delaney 2006). While pharmacologic appetite stimulants such as cyproheptidine, prednisone, benzodiazapines, mirtazapine, propofol, megesterol acetate, and even dronabinol have been utilized with varied success in the short term in veterinary patients, these measures are not feasible for long-term use as they usually do not result in the consumption of adequate amounts of calories on a sustained basis. For partially or fully anorexic patients, options include forced feeding with syringe or other method, or placement of an enteral feeding device. Forced or "assisted" feeding is a commonly utilized method that usually involves the placement of a food bolus in the rear of the oral cavity. The animal either swallows the bolus by reflex or because the mouth is held closed. Obviously, this is not ideal since it can be a stressful process for both the patient and for hospital staff, and the method is not feasible in the long term. Additionally, forced feeding can lead to choking or aspiration as well as the development of food aversions and other undesirable responses in some patients (such as aggression or fear). The placement and use of an enteral feeding device is the preferred method of providing adequate amounts of an appropriate diet, and it can be accomplished on a long-term basis with many tube types.

Fig. 20.1. Consideration of nutritional needs should be part of the management of every patient, regardless of body condition. Loss of lean body mass can be difficult to assess in obese patients in particular.

WHEN TO INTERVENE

Nutritional support should be provided as soon as malnutrition is recognized or anticipated to occur. In some cases this need will be identified and addressed at or very soon after the initial presentation. Animals with a longer history of suboptimal intakes and/or with chronic diseases in poor body condition are obvious candidates for early intervention; however, obesity is not a contraindication for nutritional support (Fig. 20.1). Other cases will require medical stabilization prior to establishing nutritional support (trauma or other emergent cases). Regardless, intervention is indicated if anorexia has been documented for longer than 3 to 5 days or if a patient is not expected to eat within 2 to 3 days (such as those with significant orofacial trauma or in need of extensive orofacial surgery).

If the need can be anticipated, it is important to initiate a discussion with the client regarding potential feeding tube use early in the course of the disease. Feeding tubes are currently a standard treatment in some common diseases, such as feline hepatic lipidosis, and they are increasingly utilized for other conditions such as renal disease, pancreatitis, and trauma. The use of most types of enteral feeding devices allows for care to continue at home even on a long-term basis, compared to parenteral nutrition, which must be administered in the hospital. However, client perceptions about feeding tubes strongly influence their acceptance of an enteral feeding device for their pet. Most people have at least a general awareness, if not first- or second-hand experience, of feeding tube use in human medicine. In most cases, clients will be aware of feeding tube use for people in vegetative states or for end-of-life

situations. The general public tends to be less aware of feeding tube use for shorter-term management of severe acute pancreatitis or adverse effects of radiation therapy of head and neck tumors. Because of this negative association, clients may not be willing to accept the placement and use of a feeding tube in their pet. They may feel that taking this step represents a point of no return or that they are giving up. People often take a unique pleasure in preparing and eating meals, and food is a large part of family and cultural identity. Most owners also enjoy feeding their pets and giving treats, and they may resist a change to what they perceive is a medical procedure, similar to administering medications. Other people may feel uncomfortable with the idea of having such a device physically associated with their pet. In this case, it may be helpful to introduce the client to patients with similar devices or to encourage them to discuss these issues with other clients who have been through the experience.

It is especially important to impress upon the client the benefits of feeding tube placement. Many sick pets are willing to eat, but they will not consume enough calories to maintain their body weight, or they will not consume a diet that is appropriate for their disease. Renal disease is a very common example, and a waxing and waning appetite is often observed in such patients. In addition to the direct physiological and physical effects of hypergastrinemia and uremia on the gastrointestinal tract, other alterations in metabolism (such as electrolyte abnormalities, altered hormonal milieu, increases in cytokines, acid-base derangements, and dehydration) can significantly impact appetite. Azotemia can also be expected to affect taste and smell perception in veterinary patients as has been reported in people (Ng, Woo et al. 2004). Additionally, many medications are known to alter smell and taste in people and this should be considered in animals as well (Bromley 2000). Many animals with renal disease will readily consume very-high-protein diets, such as chicken breast or other meats. However, restriction of protein to control the blood concentrations of uremic toxins and manage proteinuria, as well as to limit dietary phosphorus, is a major feature of nutritional therapy for these patients. Also, many animals with renal disease develop hypertension and/or fat intolerance, which can necessitate the use of an even less palatable diet restricted in protein, sodium, and fat. Provision of an appropriate diet for these patients can positively impact quality of life and improve prognosis. Additionally, feeding tube placement can facilitate the administration of extra fluids as well as medications without oral "pilling," a process that many owners and pets find unpleasant or difficult.

GENERAL CONTRAINDICATIONS

Although it is clear that providing adequate nutritional support and administering it enterally if possible is of benefit in managing many cases, most enteral feeding devices are contraindicated in patients with an increased risk of aspiration. Risk can be increased in patients that have uncontrolled vomiting, a reduced gag reflex, or a reduced level of consciousness (due to head trauma or the need to be anesthetized for assisted ventilation). However, accomplishing enteral feeding with devices that terminate in the jejunum is a viable option for some patients with an increased risk of aspiration (Shike and Latkany 1998). It is also important to consider whether frequent anesthesia or sedation may be necessary (due to bandage changes or other procedures). In this case, consideration should be given to using an enteral feeding technique that facilitates meal feeding and allows evaluation of gastric residuals (such as with imaging or aspiration), or that terminates in the jejunum.

ENTERAL FEEDING DEVICES

Enteral feeding devices include tubes that pass through the nares and end anywhere from the esophageal lumen to the jejunum; pharyngostomy tubes; esophagostomy tubes; gastrostomy tubes; duodenostomy tubes; and jejunostomy tubes. Placement of any of these tubes requires the ability to confirm correct placement into the appropriate location in the gastrointestinal tract rather than into the airway, subcutaneous space, or peritoneum. For surgically, fluoroscopically, or endoscopically placed gastrostomy, duodenostomy, or jejunostomy tubes, this confirmation can be accomplished during the placement procedure.

For other types of tubes and placement procedures, no method can confirm correct placement without doubt, particularly for tubes that terminate in the esophagus cranial to the carina. Nasoenteral or esophagostomy tube placement can be confirmed radiographically if termination is in the stomach; the tube can then be partly withdrawn into the esophagus if desired. No method is feasible for confirming correct placement in the long term. Some instances of tube displacement can be difficult to identify, such as gastrostomy tube dislodgement into the peritoneal cavity (Elliott et al. 2000). However, with experience and the use of multiple confirmatory methods, the risks of feeding through an incorrectly placed device can be reduced. Radiography can be useful; other methods to determine correct tube placement into the esophagus or stomach rather than the bronchus include the injection of air or sterile water while observing for coughing or ausculting for borborygmi. Details and excellent instructions for tube

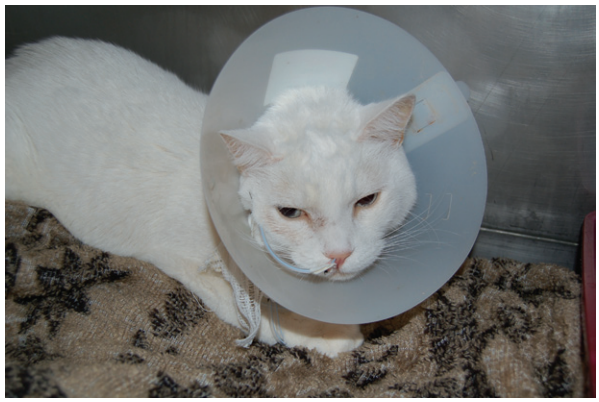


Fig. 20.2. To avoid premature removal, an Elizabethan collar must be worn by all patients with nasoenteral tubes.

placement are available elsewhere (Marks 1998; Seim and Willard 2002; Han 2004; Jergens et al. 2007). Technical aspects of enteral feeding devices will only be discussed generally here.

Nasoenteral Feeding Tubes

Nasoesophageal, nasogastric, and nasojejunal tubes are typically small diameter (5–8 French), polyurethane, polyvinylchloride, or silicone flexible tubes. Their advantages include the ability to place the tube without anesthesia or specialized equipment. These tubes can be irritating to the patient since they need to be attached to the face with suture or staples, making an Elizabethan collar necessary for the duration of use (Fig. 20.2). Nasoenteral tubes are not generally an option for at home use and are best for short-term provision of nutrients (i.e., less than 1 week; for example, in the interim between medical stabilization and placement of a more permanent tube). These tubes can also be a good option for pets with coagulopathy because no incision is necessary. While epistaxis has been reported as a potential complication during the placement of nasal tubes, refined techniques have resulted in a lower incidence (Abood and Buffington 1991) (Fig 20.3). Because general anesthesia is usually not necessary for nasoenteric tube placement, water and/or food can be administered immediately.

Pharyngostomy Feeding Tubes

Pharyngostomy tubes are sometimes used in human medicine in lieu of nasogastric tubes. Although they appear to have a low complication rate (Meehan et al. 1984; Patil

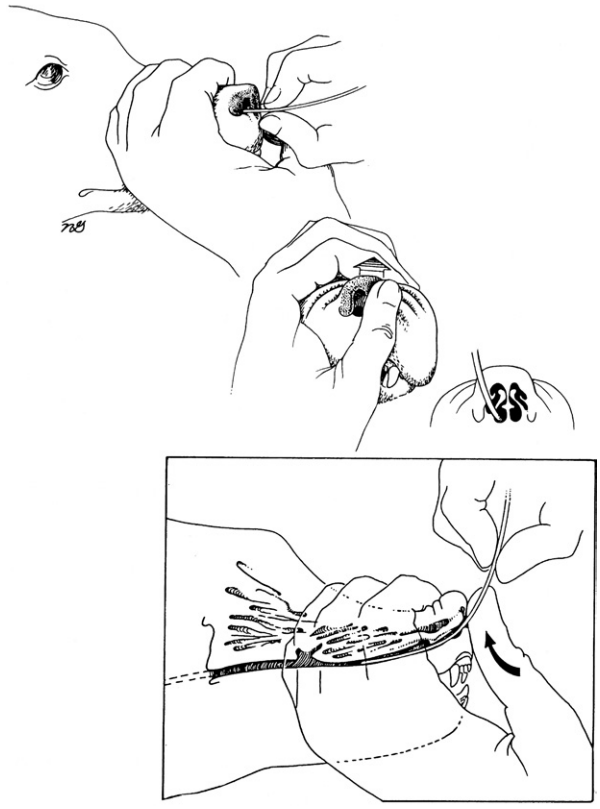


Fig. 20.3. Pushing the nares dorsally and introducing the tube at a ventromedial angle facilitates proper placement. (Used with permission from Abood and Buffington 1991.)

et al. 2006), fatal hemorrhage has been reported due to dissection of the superior thyroid artery (Edge and Langdon 1991) and their use has been recently discouraged (Vanek 2003). In veterinary medicine, pharyngostomy tube placement has no advantages over esophagostomy tube placement and can potentially result in more serious complications (Crowe and Downs 1986). Additionally, placement of a pharyngostomy tube may demand more technical skill due to the proximity of critical surrounding structures. The two tube types are similar in their indications, disadvantages, and tube sizes. For these reasons, pharyngostomy tubes have fallen out of common use.

Esophagostomy Feeding Tubes

Esophagostomy tubes are very popular in both dogs and cats. The disadvantages include the need for anesthesia for placement. However, no special equipment is necessary

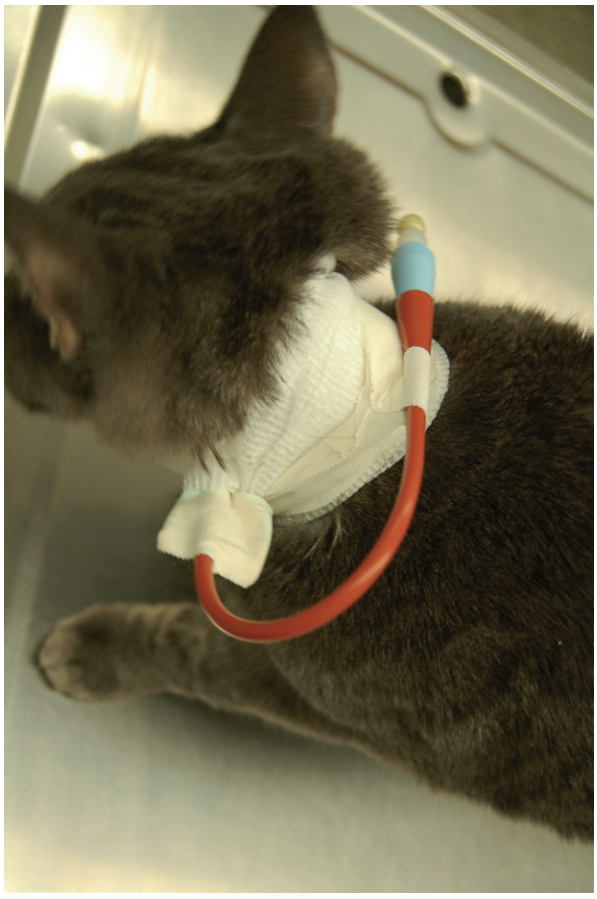


Fig. 20.4. A properly wrapped esophagostomy tube.

Fig. 20.5. The area around the stoma for a feeding tube must be kept clean and dry to prevent the development of local skin irritation or cellulitis.

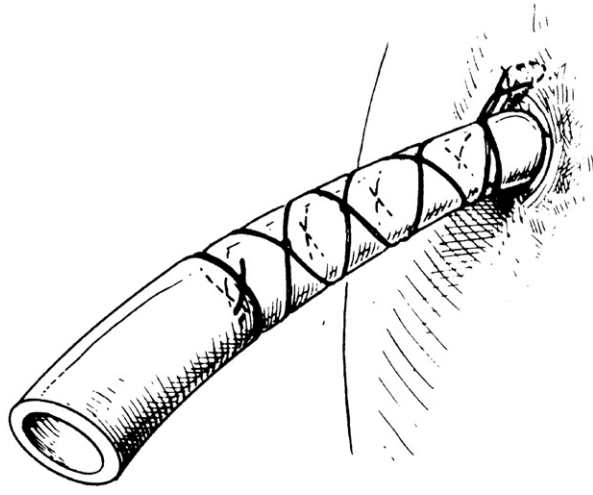


Fig. 20.6. A loosely tied anchor suture is attached to the friction suture and allows for tube replacement without repuncturing the skin. (Used with permission from Crowe 1986.)

and placement is usually inexpensive, quick, and simple (Levine et al. 1997; Han 2004). These tubes are generally very well tolerated, and only a protective neck wrap is usually necessary (Fig. 20.4). There is little danger of serious complications if the tube is removed prior to stoma formation. They are useful for home use by the client; however, care must be taken to clean and maintain the stoma site to minimize the risk of infection (Fig. 20.5). In one survey, most owners reported little difficulty with using the tube to feed their cats, and they became quite comfortable with the process with experience (Ireland et al. 2003). Complications are relatively minor and include irritation, infection, or leakage around the stoma site, obstruction of the tube with food, medications, or kinking, and vomition of the tube (Levine et al. 1997; Devitt and Seim 1997; Crowe and Devey 1997).

Typical tube types used for esophagostomy tube feeding include those composed of polyvinylchloride, polyurethane, silicone, or red rubber. Depending on tube composition these tubes can be maintained for up to 6 or 8 weeks; certain materials such as polyvinylchloride are not as durable for long-term use and replacement or removal may be required. Tube replacement is facilitated with the use of a guide wire as well as by using anchor suture that can be used to attach the new tube with a friction suture without repuncturing the skin (Fig. 20.6). Polyethylene

tubes appear to be quite irritating when compared to silicon tubes and should be avoided (Balkany et al. 1977). Tube sizes of 12–14 French are adequate for cats and small dogs while sizes 14–18 French are adequate for larger dogs. Placement of tubes too large for the patient may result in adverse effects and likely impart no more than minimal benefit over more appropriately sized tubes. A size 18-French tube caused a head tilt and circling, which resolved immediately with tube removal in one cat, while in several other instances similar tubes in cats resulted in signs of discomfort and nausea (repeated swallowing, lip licking), which also resolved with tube removal (S.J. Delaney, Veterinary Medical Teaching Hospital, University of California, Davis, personal communication). After esophagostomy tube removal, the stoma site typically heals uneventfully by second intention.

Gastrostomy Feeding Tubes

Gastrostomy tubes are particularly useful in the management of chronic diseases requiring long-term nutritional support (Fig. 20.7). One study reported canine veterinary patients being fed through gastrostomy tubes for up to 6+ years (Campbell, Marks et al. 2006). The tubes are typically latex or silicone and both traditional-length mushroom-tipped tubes as well as low-profile versions are available from a variety of manufacturers. Low-profile devices can be placed with the aid of an endoscope and may be more aesthetically pleasing to owners while reducing the risks of clogging and chewing on the tube by the pet (Campbell, Marks et al. 2006) (Fig. 20.8). Except in the smallest patients, they are large tubes (18–24 French) through which a wide variety of diets can be fed, including blenderized human food combinations as well as commercially available canned and dry diets blended with water. These devices can be placed either endoscopically [percutaneous endoscopic gastrostomy (PEG) tube], surgically (including tube gastropexy), or with a transoral rigid tube introducer (the "blind" technique). Which method is used to achieve tube placement depends on the availability of specific equipment (such as endoscopes or rigid tube introducers), the skill and training of the clinician, and patient factors. Animals with esophageal disorders, including megaesophagus and strictures, should not undergo blind placement procedures using tube introducers due to the risk of perforation or other damage to the esophagus.

The disadvantages of gastrostomy tubes include the need for anesthesia for placement and the need for specialized equipment in some cases (for endoscopic and blind placements). Most owners reported little difficulty using PEG tubes in their cats, and with experience most became comfortable with the procedure (Ireland et al. 2003). For dog owners surveyed regarding home use of a low-profile gastrostomy tube, most reported that the device was easy to use and maintain, and that the tube improved their pet's quality of life and positively impacted their life span (Yoshimoto et al. 2006; Campbell, Marks et al. 2006). One study reported no difference in PEG tube complication rate and severity when compared to esophagostomy tubes in cats (Ireland et al. 2003). Overall, complications of gastrostomy tubes range from minor to serious and include gastric bleeding during placement; improper tube placement; vomiting; irritation, infection, or leakage

Fig. 20.7. A gastrostomy tube is an excellent method of administering enteral nutritional support on a long-term basis.

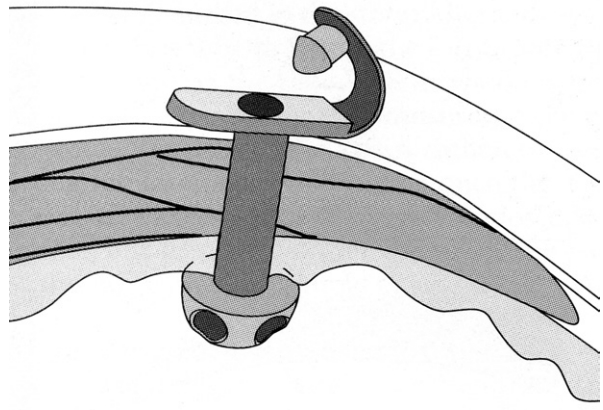


Fig. 20.8. Low-profile gastrostomy tubes may be more aesthetically pleasing for owners. (Used with permission from Marks 2005.)

around the stoma site; aspiration pneumonia; premature tube removal by the patient; and peritonitis due to displacement of the tube into the abdomen (Glaus et al. 1998; Elliott et al. 2000; Stevenson et al. 2000; Campbell, Marks et al. 2006). Although the total complication rate is high in these studies, most problems were minor and easily manageable.

Jejunal Feeding Tubes

Nasojejunal, gastrojejunostomy, and jejunostomy tubes enable post-gastric feeding. Although there are no specific indications for one intestinal location over another, placement of duodenostomy tubes is also possible (Swann, Sweet, Holt et al. 1998; Novo et al. 2001). Although the location of the stoma can be in the distal duodenum or in the proximal jejunum, the tube should terminate in the jejunum as far cranial as practical to maximize the absorptive surface area distal to the point of food introduction. The maximum recommended period for jejunal feeding device use depends partly on the tubing material. There are reports of clinical patients maintained with polyvinyl or polyurethane enterostomy tubes for up to 4 weeks (Novo et al. 2001). Another study reported the maintenance of low-profile enterostomy tubes in healthy experimental dogs for 10 months (Swann, Sweet, Holt et al. 1998).

Post-gastric feeding is useful for providing nutritional support to patients in which gastric feeding is contraindicated due to pancreatitis, severe and/or diffuse structural or physiological disease of the stomach, decreased level of consciousness, proximal obstruction, delayed gastric emptying, or intractable vomiting. A study in people with severe acute pancreatitis compared nasogastric and nasojejunal tube feeding; no differences were found in adverse effects or clinical outcomes (Kumar et al. 2006). However, because gastric emptying is often delayed secondary to pancreatitis, post-gastric feeding is often a feasible alternative (Meier et al. 2006). Also, stimulation of pancreatic secretion is significantly decreased in healthy people in response to a liquid meal infusion into the jejunum compared to into the stomach, probably secondary to a reduced and delayed hormonal response [gastrin and cholecystokinin (Czakó et al. 1999)]. Similar results have been found in dogs; gastric and duodenal nutrient infusions caused an increase in pancreatic secretion, while jejunal infusions did not (Ragins et al. 1973). When parenteral nutrition was compared with jejunal nutrition in a dog model of severe acute pancreatitis, enteral feeding was associated with decreased endotoxin and bacterial translocation and did not cause worsening of pancreatic pathology (Qin et al. 2002). In people with pancreatitis, early enteral feeding via the jejunal route is safe and is recommended in this context due to cost effectiveness compared to parenteral nutrition (McClave, Greene et al. 1997). Whenever possible, it is advisable to provide nutritional support enterally in veterinary patients with pancreatitis, and to deliver the nutrients jejunally to reduce pancreatic stimulation.

Nasojejunal tubes are typically size 5–8 French polyurethane tubes with weighted tips. One advantage of nasojejunal tubes is that sedation or anesthesia is usually not necessary for placement. Verification of correct placement can be accomplished with fluoroscopic guidance (Wohl 2006), or with attempts to aspirate insufflated air (Harrison et al. 1997). Choosing a tube that includes a radio-opaque marker is useful for facilitating the verification of correct placement and for monitoring potential tube migration; however, this can also be accomplished with the injection of contrast material.

Gastrojejunostomy tubes consist of smaller diameter tubes (12 French) fed through larger bore gastrostomy tubes (Fig. 20.9). General anesthesia is required for the placement of gastrojejunostomy tubes and generally also for enterostomy tubes; however, one study reported successful placement of duodenostomy tubes with only sedation in a small number of animals (Novo et al. 2001). Gastrojejunostomy tubes can be useful in cases that initially require post-gastric feeding but that may benefit from transition to enteral feeding directly into the stomach (Jennings et al. 2001). Also, if endoscopy or a blind

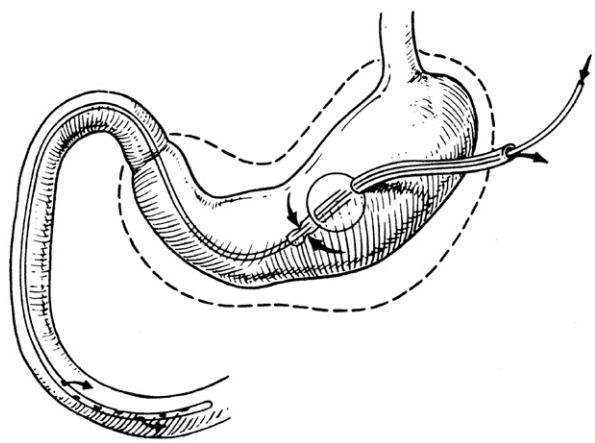


Fig. 20.9. A small gauge tube terminating in the small intestine can be placed through a larger gastrostomy tube. (Used with permission from Crowe and Downs 1986.)

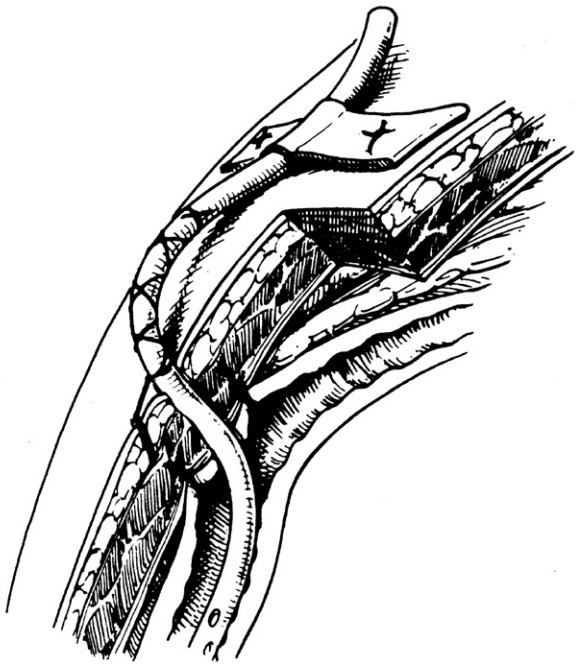


Fig. 20.10. After a purse-string suture is placed in the intestinal serosa, the enterostomy site is attached to the abdominal wall. (Used with permission from Crowe and Downs 1986.) Some authors also advocate a serosal fold-over to create an elongated pocket for tunneling of the tube prior to exiting the body wall (Delany et al. 1973).

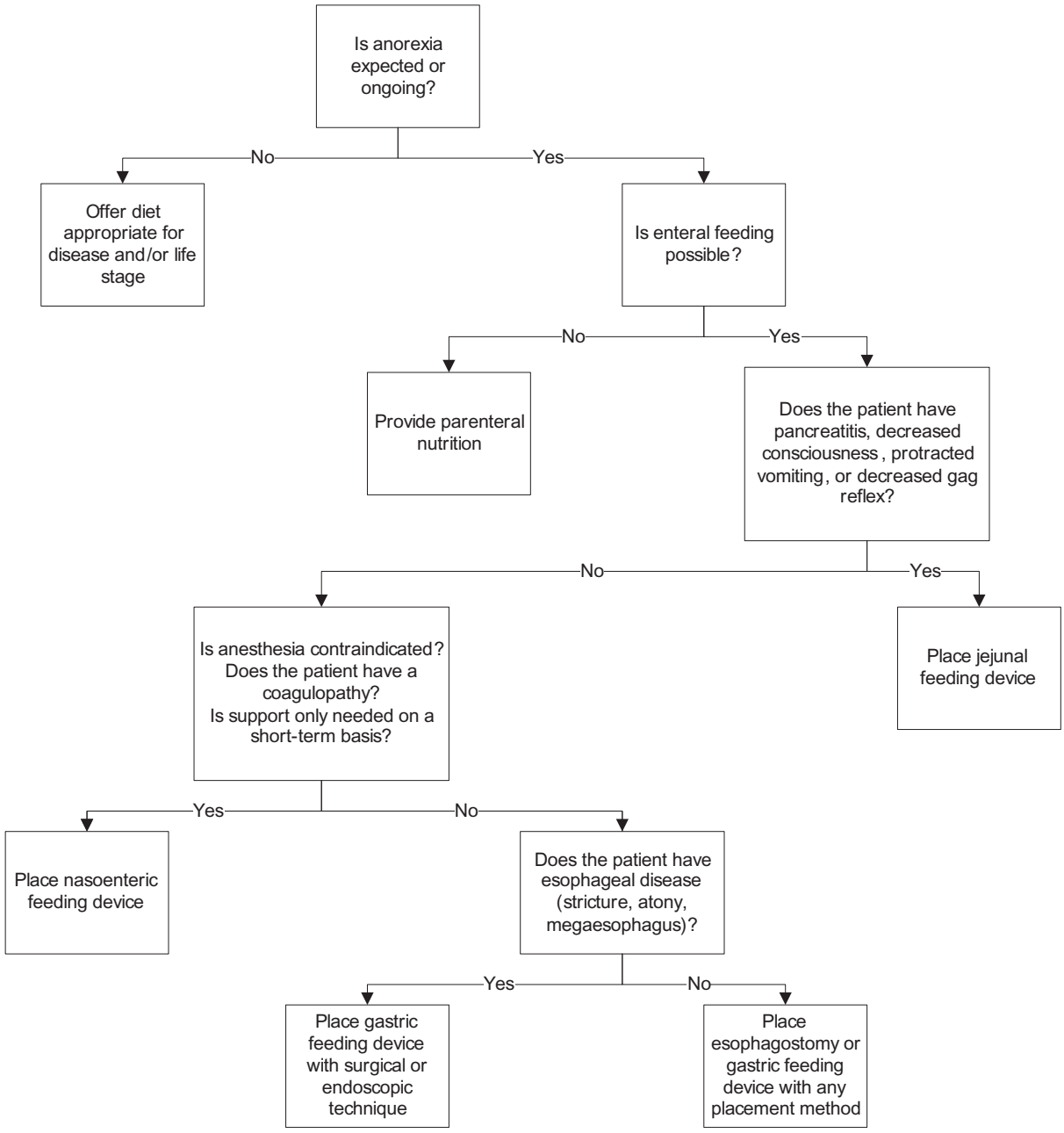
technique is used to place this type of dual tube, surgery can be avoided (Jergens et al. 2007).

Enterostomy tubes are usually red rubber or silastic feeding tubes, although low-profile devices are also available (Swann, Sweet, and Michel 1997; Swann, Sweet, Holt et al. 1998). Jejunostomy tubes can be successfully placed with either surgical or laproscopic techniques (Hewitt et al. 2004) (Fig. 20.10). As human patients are likely less mobile than critically ill veterinary patients, migration may be a greater issue in dogs and cats. Also, tubes in veterinary patients are maintained in a more horizontal position even during activity. Some types of jejunal feeding devices have weighted tips to help achieve correct tube placement and to discourage retrograde movement. However, a prospective trial in humans showed that unweighted nasoenteral tubes traversed the pylorus into the intestine more often and more rapidly than weighted tubes (Lord et al. 1993). Also, a study investigating gastrojejunostomy tubes in dogs reported that correct placement of the distal catheter tip was important to avoid retrograde movement when using unweighted tubes (Jergens et al. 2007). It appears that weighted tips are not necessarily critical either for self-advancing nasojejunal tube placement or for maintenance of proper positioning of jejunal tubes. Reported complications of jejunal feeding include premature tube removal, retrograde tube movement, diarrhea, vomiting, focal cellulitis, leakage of gastrointestinal contents, and tube obstruction (Swann, Sweet, and Michel 1997; Swann, Sweet, Holt et al. 1998; Wohl 2006; Jergens et al. 2007).

BEGINNING ENTERAL FEEDING

An initial first meal for veterinary patients with an enteral feeding device will be a liquid diet or a slurry of canned food, dry food, or a combination of human foods (such as cottage cheese and rice). With nasoenteric tubes placed without general anesthesia, feeding can be commenced immediately. For esophagostomy and gastrostomy tubes, water and food can be introduced via the new tube as soon as the patient is fully recovered from anesthesia. Typically, water is introduced first to ensure the patient's tolerance prior to introducing a first meal. For gastrostomy tubes, it has been commonly advised that food and water be given only after a period of 12 to 24 hours (Han 2004). Presumably the rationale is that the placement procedure may interfere with normal gastric motility, increasing the risk of aspiration or leakage. However, controlled studies in people have shown that initiation of feeding within 4 hours of PEG tube placement is not associated with increased morbidity compared to the traditional protocol of waiting for up to 24 hours (Choudhry et al. 1996; McCarter et al. 1998; Dubagunta et al. 2002), even in critically ill patients (Stein et al. 2002). There are no such published studies in animals; however, it is known that the presence of a gastrostomy tube does not delay gastric emptying rate in healthy cats measured at 1 day post placement (Smith et al. 1998). Unlike human patients, veterinary patients must be anesthetized for the placement of such devices. There appears to be no reason to wait related to the gastrostomy device itself; however, depending on the anesthetic protocol and the patient, full recovery may take up to 24 hours.

In more debilitated patients, and perhaps in cases where tube placement proves difficult and is prolonged, it may be best to initiate feeding in a more conservative fashion. In these patients, 25% to 33% of the daily caloric requirement should be fed the first day over four to six meals, then 50% to 67% the second day and so on. Alternatively, nasoenteric, esophagostomy, or gastrostomy tube feeding can be accomplished with a constant rate infusion as in



Flowchart 20.1. Decision-making process for type and method of nutritional support for veterinary patients.

jejunal feeding; both methods result in delivery of adequate energy without gastrointestinal complications (Campbell, Jutkowitz et al. 2010, Holahan et al. 2010). Of course, the rate of weaning up to full caloric requirements will vary with underlying disease, body condition, length of anorexia and risk of refeeding syndrome, and level of patient-monitoring abilities. In many cases, it is best if the patient can stay in the hospital long enough to assess tolerance of feeding the entire amount of the daily caloric requirement. This is also a good time to teach the owner

about feeding tube care and to encourage participation in some or all of the feedings. The owner should understand the importance of initially feeding at a slow rate to reduce the incidence of nausea and vomiting. Some hospitalized patients may show volume intolerance in response to assisted enteral feeding. Most dogs and cats will tolerate meal sizes of 5–10 ml per kg of body weight after a period of fasting (Remillard, Armstrong et al. 2000). The rate and/or volume should be decreased if drooling, retching, swallowing, or vomiting is noted during a feeding. If necessary, promotility agents can be administered in some cases to facilitate successful tube feeding (e.g., erythromycin, ranitidine, cisapride, metoclopramide). In people, such medications are recommended only for patients with evidence of intolerance of enteral feeding (Kreymann et al. 2006). Over time, the patient should begin to tolerate larger and less frequent meals; this can usually accommodate a reasonable feeding schedule at home.

DIET CHOICES

There is no one best diet for use with enteral feeding devices, and there are many options. Factors to be considered when choosing a diet include not only tube size but also caloric density, macronutrient distribution, particle size, osmolarity, ingredients, cost, and availability. It is also important to consider the expected period of feeding and whether the diet chosen is complete and balanced for the individual patient. For many patients, the underlying disease will limit the choices to diets that incorporate specific, appropriate modifications (renal or hepatic disease, fat intolerance). In some cases, tube size will limit diet choices to those of a particular viscosity (i.e., liquid diets for nasoenteric or enterostomy tubes). If possible, providing a complete and balanced commercially available diet is preferable. This includes slurries of blenderized canned or dry diets; however, both commercially available and home-prepared options are available.

A wide range of both canned and dry foods can be fed enterally. For slurries of commercially available diets, it may be necessary to experiment with different water ratios to achieve the desired consistency that will easily flow through the selected tube. Maintaining a supply of different tube types and sizes for testing is useful. This will help avoid tube obstructions and aid in calculation of caloric density of specific diet slurries. It is best to blenderize the slurry for sufficient time to achieve a smooth consistency. Due to the time needed for this process and the potential for incorporation of some air into the slurry, the caloric density can only be accurately calculated by measuring the volume of the final slurry (i.e., the total volume may not be additive from the volume of diet and water).

It is helpful for the clinician to have a basic understanding of the characteristics of a range of different prescription diets. For example, knowing which renal therapeutic or uncommon antigen diets are lowest in fat can be useful. Note that pet food manufacturers are frequently developing new products or modifying the formulations of existing diets, and it may be difficult for most practitioners to remain up-to-date on current information. In general, an appropriate diet may be chosen on the basis of the caloric distribution (percent of calories from fat, protein, and carbohydrate), micronutrient levels (phosphorus or sodium restriction, profile compared to patient's requirements), and ingredient source. Consider commercially available pet food options and human enteral formulas as well as homemade diets. For fat-intolerant animals, cottage cheese and rice slurries are useful for tube feeding, and can be supplemented with a linoleic acid source and micronutrients as necessary for longer term feeding. Likewise, homemade uncommon antigen diets for patients with specific needs can be used; for example, a slurry of canned crab and pasta can be used for fat-intolerant patients with inflammatory bowel disease or patients with lymphangiectasia.

Liquid diets are available that are marketed both for human and veterinary patients. They are the sole option for patients with small diameter feeding tubes (nasoenteric and jejunal tubes). Such diets are generally well tolerated and can provide adequate nutrients to facilitate weight maintenance in hospitalized patients (Abood and Buffington 1992). Additionally, some animals will voluntarily consume a liquid diet while rejecting solids. Despite a range of variables (including patient disease state and life stage, method of administration, and consumption of various other diets), one prospective uncontrolled study of hospitalized dogs and cats reported few complications and a satisfactory success rate with the use of commercially available liquid diets (Crowe, Devey, Palmer et. al. 1997). These diets tend to be expensive, especially in larger patients, and it is important to note that most commonly used liquid diets do not meet every currently known nutrient requirement of dogs and cats. Trace minerals, vitamin K, cobalamin, and choline are the most commonly deficient nutrients (Table 20.1). These may not be likely to result in clinically significant nutritional deficiency when fed for a short time; however, supplementation with parenteral cobalamin and vitamin K may be indicated in patients undergoing antibiotic therapy due to a decreased supply of these vitamins from intestinal

Table 20.1. Nutrient Comparisons of Commonly Used Liquid Diets With NRC Recommended Allowances[1]

Energy Density (kcal/ml)	CliniCare[2]	CliniCare RF[2]	Ensure[3]	Ensure HP[3]	Vivonex Plus[4]	Vital HN[5]	Feline adult allowance	Canine adult allowance
	1.00	1.00	1.06	0.97	1.00	1.00		
Calorie Content (ME)								
Protein %ME	30	22	14	21	18	16.7	(/1,000 kcal)	(/1,000 kcal)
Fat %ME	45	57	22	24	6	9.5		
CHO %ME	25	21	64	55	76	73.8		
Osmolality (mOsm/kg H_2O)	310	235	620	610	650	500		
Crude Protein (g/1,000 kcal)	82	63	36	52	45	41.7	50	25
Arginine (g/1,000 kcal)	3.5	3.5	1.56	2.02	5	2.09	1.93	0.88
Histidine (g/1,000 kcal)	unknown	unknown	0.91	1.35	0.9	1.08	0.65	0.48
Isoleucine (g/1,000 kcal)	unknown	unknown	1.79	2.33	3.38	1.96	1.08	0.95
Leucine (g/1,000 kcal)	unknown	unknown	3.55	4.61	6.75	3.25	2.55	1.7
Lysine (g/1,000 kcal)	unknown	unknown	2.63	3.63	2.79	2.29	0.85	0.88
Methionine & Cystine (g/1,000 kcal)	unknown	unknown	1.20	1.61	2.48	1.33	0.85	1.63
Methionine (g/1,000 kcal)	unknown	unknown	0.90	1.30	1.35	0.92	0.43	0.83
Phenylalanine & Tyrosine (g/1,000 kcal)	unknown	unknown	3.41	4.98	4.05	3.33	3.83	1.85
Phenylalanine (g/1,000 kcal)	unknown	unknown	1.87	2.54	2.84	1.83	1	1.13
Taurine (g/1,000 kcal)	0.63	0.63	0	0	0.07	0	0.1	0
Threonine (g/1,000 kcal)	unknown	unknown	1.58	2.13	1.89	1.58	1.3	1.08
Tryptophan (g/1,000 kcal)	unknown	unknown	0.47	0.62	0.68	0.50	0.33	0.35
Valine (g/1,000 kcal)	unknown	unknown	2.24	2.80	3.38	2.25	1.28	1.23
Total Fat (g/1,000 kcal)	51	67.5	24	26	6.7	10.8	22.5	13.8
Arachidonic Acid (g/1,000 kcal)	0.1	0.13	unknown	unknown	unknown	0.06	0.02	0
EPA & DHA (g/1,000 kcal)	0.65	0.78	unknown	unknown	unknown	0	0.03	0.11

Continued

Table 20.1. *Continued*

Energy Density (kcal/ml)	CliniCare[2]	CliniCare RF[2]	Ensure[3]	Ensure HP[3]	Vivonex Plus[4]	Vital HN[5]	Feline adult allowance	Canine adult allowance
	1.00	1.00	1.06	0.97	1.00	1.00		
Linoleic Acid (g/1,000 kcal)	18.48	23.47	unknown	unknown	5.13	3.99	1.4	2.8
α-Linolenic Acid (g/1,000 kcal)	13.9	3.14	unknown	unknown	0.73	0.08	0	0.11
Minerals								
Calcium (g/1,000 kcal)	1.47	1.24	1.2	1.2	0.56	0.67	0.72	1
Chloride (mg/1,000 kcal)	1,150	620	1,120	1,500	940	1,032	240	300
Chromium (mcg/1,000 kcal)	0	0	120	120	67	67	0	0
Copper (mg/1,000 kcal)	2.1	1	2	2	1.1	1.4	1.2	1.5
Iodine (ug/1,000 kcal)	500	70	148	152	89	100	350	220
Iron (mg/1,000 kcal)	25	17	18	18	10	12	20	7.5
Magnesium (mg/1,000 kcal)	115	93	400	400	220	267	100	150
Manganese (mg/1,000 kcal)	3.4	2.5	4.8	5.2	1.1	3.4	1.2	1.2
Phosphorus (g/1,000 kcal)	1.26	1.03	1	1	0.56	0.667	0.64	0.75
Potassium (g/1,000 kcal)	1.68	1.24	1.48	2	1.06	1.4	1.3	1
Selenium (mcg/1,000 kcal)	40	30	68	72	39	47	75	87.5
Sodium (mg/1,000 kcal)	840	620	800	1160	610	566	170	200
Zinc (mg/1,000 kcal)	35	15	14.8	22.8	13	15	18.5	15
Vitamins								
Biotin (mcg/1,000 kcal)	422	400	300	300	330	400	18.75	0
Cholecalciferol (ug/1,000 kcal)	7.5	8.75	16	10	5.5	6.7	1.75	3.4
Choline (mg/1,000 kcal)	550	500	328	400	220	400	637	425
Cobalamin (mcg/1,000 kcal)	6.5	6.5	6	6	6.7	8	5.6	8.75
Folic acid (ug/1,000 kcal)	1,000	1,000	400	400	440	533	188	67.5
Niacin (mg/1,000 kcal)	13.75	13.5	20	20	22	26.7	10	4.25

Table 20.1. *Continued*

Energy Density (kcal/ml)	CliniCare[2]	CliniCare RF[2]	Ensure[3]	Ensure HP[3]	Vivonex Plus[4]	Vital HN[5]	Feline adult allowance	Canine adult allowance
	1.00	1.00	1.06	0.97	1.00	1.00		
Pantothenic acid (mg/1,000 kcal)	8.8	8.8	10	10	11	13.4	1.44	3.75
Pyridoxine (mg/1,000 kcal)	1.3	1.3	2	2	2.2	2.7	0.625	0.375
Riboflavin (mg/1,000 kcal)	2.6	2.6	1.72	1.72	1.9	2.3	1	1.3
Thiamin (mg/1,000 kcal)	2.6	2.6	1.52	1.52	1.7	2	1.4	0.56
Vitamin A (mcg retinol/1,000 kcal)	600	600	1667	1500	834	999.6	250	379
Vitamin E (α-tocopherol) (mg/1,000 kcal)	22	10	30	32.2	11.39	30	10	7.5
Vitamin K (Menadione) (mg/1,000 kcal)	0.04	0.04	0.08	0.08	0.044	0.05	0.25	0.41

[1]*Nutrient Requirements of Dogs and Cats*. 2006. Washington, DC: National Academies Press.
[2]CliniCare® Canine/Feline Liquid Diet and CliniCare® RF Feline Liquid Diet; Abbott Animal Health, Abbott Park, IL, USA.
[3]Ensure® Nutrition Shake and Ensure® High Protein Shake; Abbott Nutrition, Columbus, OH, USA.
[4]Vivonex® Plus; Nestlé HealthCare Nutrition, Gland, Switzerland.
[5]Vital® HN; Abbott Nutrition, Columbus, OH, USA.

microbial synthesis. Also, vitamin K supplementation should be considered in patients with severe cholestasis, extrahepatic bile duct obstruction, or other disorder resulting in impaired bile secretion and reabsorption.

Liquid diets can be classified as monomeric (elemental) or polymeric (nonelemental). Monomeric formulations contain amino acids and/or short peptides (typically hydrolysates of protein isolates) in addition to simple carbohydrates (mono- and disaccharides). Polymeric formulations contain longer peptide chains or complete proteins as well as more complex carbohydrates (starches). In order to provide a reasonable caloric density, liquid veterinary diets are generally high in fat (up to 57% of calories). High-fat diets are contraindicated in some cases (i.e., pancreatitis, lymphangectasia, or other intestinal diseases). However, some human enteral formulations provide comparable energy while restricting fat; these are acceptable alternatives for fat-intolerant patients (Table 20.1). However, for feline patients, note that many human enteral liquid diets are not supplemented with taurine and some contain fructose, high concentrations of which should be avoided in cats due to resultant fructosuria (Droucher and Muller-Schlosser 1980). Additionally, some formulations may contain medium-chain triglycerides (MCTs), which are reported to be of potential benefit in patients with malabsorption syndromes, but may be contraindicated in feline patients (NRC 2006). One study that investigated the effects of essential fatty acid deficiency reported increased fat deposition in the livers of cats fed MCTs [in the form of hydrogenated coconut oil (HCO)] despite adequate dietary linoleate (MacDonald, Rogers et al. 1985). However, body weight and food intake data were not

reported, and subsequent studies demonstrated a significant decrease of both food intake and body weight gain of kittens fed similar levels of HCO, apparently due to strongly negative palatability of this fat source (MacDonald, Rogers et al. 1985). Thus, the development of excessive fat accumulation in the livers of cats fed MCTs may be the result of poor food intake secondary to low palatability rather than being caused by the MCTs per se. Suboptimal energy intake is a well-established risk factor for the development of feline hepatic lipidosis. Indeed, more current research has found no feed refusal by healthy cats when fed MCT-containing diets, and effects on lipid metabolism were minimal (Trevizan et al. 2010). The reason for the conflicting results is unknown. Although assisted enteral feeding would overcome palatability problems, and MCTs appear safe, their efficacy has not been established for any disease at this time.

IMMUNOMODULATING NUTRIENTS

Enteral formulas are increasingly supplemented with nutrients purported to promote gut health, speed healing, and/or modulate immune and inflammatory responses. There are several nutrients with a proposed direct benefit to the intestinal tract, including glutamine, arginine, omega-3 fatty acids, and short-chain fatty acids. Such diets have been associated with improved outcomes in people (Wu et al. 2001). Although these nutrients have been the focus of intense investigation in the human medical literature (including the use of rodent and canine models), there is a dearth of scientific investigation of the effects of these nutrients in dogs and cats with naturally occurring disease.

Glutamine

Glutamine is a dispensable amino acid that has important metabolic roles. It serves as a vehicle of nitrogen transport, a precursor of glucose and glycogen, and is a substrate in the urea cycle and in nucleotide synthesis. Glutamine is also used preferentially by enterocytes as an energy source, and under states of catabolic stress it is considered conditionally essential. It has been demonstrated that glutamine may be important for preventing bacterial or endotoxin translocation, reducing villus blunting and destruction, and maintaining normal enterocyte function when administered orally or parenterally to animal models (O'Dwyer et al. 1989; Chen, Okuma et al. 1994; Houdijk et al. 1998; Boza et al. 2001). Some studies have shown that glutamine supplementation of enteral formulas for human patients is safe and even beneficial in terms of overall morbidity and mortality (Wischmeyer et al. 2001; Garrel et al. 2003). However, enteral glutamine supplementation has not been consistently demonstrated to improve overall outcomes in human ICU patients (Conejero et al. 2002; Schulman et al. 2005). Additionally, a prospective study in cats with experimentally induced enteritis did not show a superior protective effect of glutamine supplementation (Marks, Cook et al. 1999). Due to the inconclusive body of evidence for the benefits of glutamine supplementation for gastrointestinal disease in people, routine use has not been recommended (Lochs et al. 2006).

While routine use of glutamine supplementation in certain diseases is discouraged in human medicine due to a lack of convincing efficacy data, the practice appears to be safe. However, in patients with renal or hepatic disease, it must be considered that additional glutamine at sometimes pharmacological doses will contribute a significant nitrogen load and should be avoided. Free glutamine is unstable in solution, which precludes its use in many parenteral and enteral formulations; however, glutamine dipeptides such as alanyl-glutamine in parenteral formulas have been shown to be equally efficacious at maintaining nitrogen balance, plasma glutamine levels, villus area, and intestinal mucosal thickness in rats and dogs (Jiang et al. 1993). Glutamine dipeptides are increasingly present in both parenteral and enteral human formulations (Zheng et al. 2006; Lima et al. 2007).

Arginine

Arginine is an essential amino acid for dogs and cats. It is considered conditionally essential in growing infants and during critical illness. Supplementation of human enteral formulations with arginine is not uncommon, so the use of these products in animals typically does not require enrichment (Table 20.1). While still controversial, arginine supplementation has been demonstrated to help maintain immune function and improve wound healing in some circumstances (Stechmiller et al. 2005; Marin et al. 2006). Because it is also important as a precursor of nitric acid, some research has explored its potential benefit in shock resuscitation (Yan et al. 2007). Although promising, thus far data regarding the use of arginine in human patients do not suggest a definitive benefit. There has been some work in the area of using arginine therapeutically for neoplasia; however, further research is needed to define safety and efficacy (Ma et al. 2010). Investigations of its use in clinical veterinary medicine are lacking. One study in dogs with lymphoma suggests that high concentrations of arginine fed in combination with omega-3 fatty acids increased survival times (Ogilvie et al. 2000); however, another study of human breast cancer patients suggests that supplemental arginine may increase protein synthesis within

tumor cells (Park et al. 1992). Additionally, due to competition for transport processes between these two basic amino acids, excessive arginine supplementation may lead to increased urinary losses of lysine. Due to the apparent high dose necessary to achieve benefit, and the lack of specific conclusive evidence of safety and efficacy, supplementation should be done with caution (Wilmore 2004). Until more convincing data are published to support the use of high-dose arginine in animals, supplementation beyond satisfaction of requirements cannot be recommended in critically ill veterinary patients.

Other Nutrients

There are several other nutrients of interest in the management of critical illness in animals and people. These include omega-3 fatty acids, short-chain fatty acids, choline, nucleotides, and various antioxidants. There are excellent reviews of the therapeutic use of many of these nutrients elsewhere (LeLeiko and Walsh 1996; Hickman 1998; Michel 1998; Simpson 1998). Despite some promising data from human trials and rodent models, there is no definitive evidence for a beneficial therapeutic effect for most of these nutrients in naturally occurring clinical diseases of veterinary patients. Probably the most convincing data are from investigations of the effects of short-chain fatty acids on intestinal health (i.e., butyrate, proprionate, and acetate). Sources of these compounds include fructooligosaccharides (FOSs) and fermentable fibers such as pectins and gums. There is considerable debate in the human medical literature regarding the relationship between dietary fiber and intestinal microflora, and the role of this relationship with respect to intestinal health, colon cancer, and inflammatory bowel diseases (Lupton 2004; Lim et al. 2005; Rose et al. 2007). Although most work has been focused on large intestinal disease, effects of fermentable fibers and FOSs are also likely to impact the small intestine due to increases in intestinal content viscosity and alterations in intestinal motility and nutrient absorption. Because of this, addition of fermentable fiber and/or FOSs to the dietary management plan of any patient with critical illness or any other less severe systemic disease that results in altered intestinal function should be considered.

CALCULATION OF ENERGY REQUIREMENTS

It is believed that sick patients have increased requirements for energy and other nutrients. Additionally, it has been demonstrated that critically ill dogs catabolize significant amounts of endogenous protein [i.e., lean body mass (Michel, King et al. 1997)]. Physiological stress from trauma and illness enhances skeletal muscle breakdown by several mechanisms (Hasselgren and Fischer 2001). Because of this, animals that are anorexic due to disease are likely to become malnourished to a greater degree in a shorter time than healthy animals deprived of food. Although illness factors have been used in the past to account for these increased needs, it is now recognized that such factors may overestimate the requirements of convalescing, recumbent, and inactive veterinary patients (Walton et al. 1996; Chan 2004). There are potentially adverse consequences to overfeeding, and there is general agreement that this should be avoided in veterinary patients despite few published scientific investigations. One study showed similar outcomes in hospitalized dogs and cats that were provided higher amounts of energy compared to approximately basal requirements (Brunetto et al. 2010). Although randomized prospective clinical trials have not yet been done in people, the European Society for Clinical Nutrition and Metabolism Guidelines on Enteral Nutrition advises against providing more than approximately basal energy requirements, especially in the acute phase of critical illness (Kreymann et al. 2006). This is partly because some evidence shows that achieving caloric intakes below calculated target values may improve outcomes in some patients (Krishnan et al. 2003).

The true metabolic energy requirement (MER) of veterinary patients is often not known, so the calculated needs can over- or underestimate actual requirements. MER is calculated by first determining the resting energy requirement (RER): $Wt_{kg}^{0.75} \times 70$), then multiplying by a factor depending on species and neuter status. To avoid overfeeding hospitalized patients with potentially wide variations in true MER, it is best to start with RER, monitor body weight, and adjust the amount fed if necessary (Table 20.2). This approach allows for any necessary adjustments while avoiding potentially adverse effects of hyperalimentation (Chan 2004).

COMPLICATIONS

Complications of assisted enteral feeding include those in the categories of mechanical (tube obstruction, leakage, or displacement), metabolic (refeeding syndrome, local infection or abscess) and gastrointestinal (vomiting and diarrhea).

Mechanical Complications

Smaller diameter and more flexible tubes (silicon) are more prone to obstruction due to food or medication clogs or kinking. Liquid diets are necessary for feeding through nasoenteral and enterostomy tubes due to their small inner

Table 20.2. Example Calculations for Feeding a Hospitalized Canine Patient

20 kg canine patient with esophagostomy tube

RER = $20^{0.75} \times 70 = 662$ kcal per day

Desired diet provides 1.25 kcal per ml when adequately blended for tube feeding

Volume to feed at full RER: 662 kcal per day/1.25 kcal per ml = 530 ml per day

Volume per meal when feeding 4 meals per day:
530 ml per day/4 meals per day = 133 ml per meal

Day 1: Start at 25% of RER (166 kcal)
Feed 33 ml per meal over 4 meals for a total of 133 ml per day

Day 2: Increase to 50% of RER (331 kcal)
Feed 66 ml per meal over 4 meals for a total of 266 ml per day

Day 3: Increase to 75% of RER (497 kcal)
Feed 99 ml per meal over 4 meals for a total of 398 ml per day

Day 4: Increase to 100% of RER (662 kcal)
Feed 133 ml per meal over 4 meals for a total of 530 ml per day

Monitor body weight and adjust amount fed as needed to achieve target condition

Account for water requirements if patient cannot consume water voluntarily

Water sources include diet, water for blenderizing, and water for flushing tube

Patient requires 662 ml water per day for maintenance requirements,
estimated using RER equation: $20^{0.75} \times 70 = 662$ ml per day

Example diet is 80% moisture and provides 1,500 kcal per kg as fed

662 kcal per day/1,500 kcal per kg = 0.441 kg per day

Patient requires 441 grams as fed per day to meet energy needs

441 grams of diet provides 353 grams (353 ml) of water
441 grams * 80% = 353 grams = 353 ml

For adequate blenderizing, example diet requires 25 ml water per 441 grams.
For tube flushing, use 10 ml after each feeding

Water from diet (353 ml + 25 ml per day) + water from flushing (40 ml per day) = 418 ml per day
Deficit of 244 ml per day (662 ml − 418 ml) must be provided through the tube
Monitor hydration status by checking urine specific gravity, skin turgor, and mucus membrane character, and adjust as needed

lumen. Feeding other types of diets through these devices will increase the risk of tube obstruction. To prevent tube clogging in meal-fed patients, water should be flushed through the tube after feeding or administration of medication. The tube end should be capped or closed to ensure that a water column is left in the tube lumen. It is important to know how much water is necessary to thoroughly flush the tube, and to account for this added water when calculating the total amount of water needed by and given to the patient. If a clog occurs, gentle repeated suction and aspiration should be attempted initially. To clear more stubborn obstructions, various methods have been devised. Infusion of a carbonated, nonalcoholic beverage, commercially available pancreatic enzyme product, or meat tenderizer can be attempted to break up the coagulated material in the tube lumen (Marcuard and Stegall 1990;

Marks 1998; Seim and Willard 2002). Another option is to introduce a guidewire or endoscopy forceps through the tube to physically dislodge the clogged material. If these attempts fail, tube replacement is necessary.

Leakage of gastric secretions or food out of the tube can occur. It is important to keep the area around the stoma clean and dry to prevent skin irritation and the development of cellulitis. Owners using enteral feeding devices at home should be counseled regarding maintenance and monitoring of the stoma site. Topical antibiotic ointments are usually applied to the stoma during healing; however, oral antibiotics and/or tube removal may be necessary if infection develops.

The displacement of an enteral feeding device can have a range of potential consequences. A nasoenteric tube pulled out of the nares can simply be replaced if necessary. If an esophagostomy tube is inadvertently removed from the outside, consequence to the patient is minimal even if an esophageal stoma has not yet formed. However, a potentially disastrous outcome can occur if a nasoenteric or esophagostomy tube is vomited out through the mouth (Seim and Willard 2002; Han 2004). The animal can sever the end of the tube and swallow or aspirate it, necessitating a surgical or endoscopic procedure. An esophagostomy tube should be replaced under heavy sedation or anesthesia to avoid positioning the tube in the subcutaneous space or in the mediastinum (Han 2004). Displacements of gastrostomy or enterostomy feeding devices may lead to peritonitis if this occurs soon after tube placement. Clearly, such tubes must be protected from damage by the patient. Determined pets and/or inattentive hospital staff or owners can create a potentially life-threatening situation. The use of Elizabethan collars, wrap bandages, stockinettes, and similar barrier devices is required, at least initially.

To avoid the risk of peritonitis, a mature fistulous tract is required for removal of the feeding device. Animals with impaired ability to heal (severe debilitation, hypoproteinemia, hyperadrenocorticism, immunosuppressive medications) may take more time for the formation of a complete stoma. In people, inadvertent removal of the tube within 7 days of placement is an indication for immediate laparotomy or endoscopic tube replacement; however, when the tube is no longer needed, the stoma is typically left to mature for up to 3 months prior to removal (Galat et al. 1990; Blocksom et al. 2004). In veterinary patients, formal guidelines for minimum intervals before gastrostomy tube removal have not been developed. Typical recommendations are usually to avoid tube removal for at least 7 to 14 days (Marks 1998; Han 2004). Because the consequences of gastric content spillage into the peritoneal space are serious, a conservative approach is advised for voluntary tube removal. However, some dogs and cats will remove their tubes despite the judicious use of barriers such as Elizabethan collars. If the tube is chewed, a portion of the tube may be left in the gastric lumen and pose a risk for intestinal obstruction. These patients must undergo endoscopy or laparotomy to remove this foreign body before obstruction occurs. Emergency surgery is clearly indicated in all animals if the tube is removed by the patient in the first 7 to 10 days following placement. If the tube is removed during the interval between this initial period and several weeks, the potential consequences are less clear. Injection of contrast material into the feeding tube or through the fistula is a noninvasive way to confirm leakage into the peritoneal space with radiography. One study reported "complete but thin" gastrocutaneous fistulas found on necropsy of 4 out of 12 healthy cats as far out as 49 to 63 days post placement, although other cats in the study had adequate adhesions as early as 11 days post placement (Stevenson et al. 2000). The authors postulated that increased movement of the device resulting from the animal's activity may have delayed maturation of the fistula, especially the portion adjacent to the abdominal wall. Another study investigating fistulous tract formation in dogs reported that closer apposition of the serous surface of the stomach to the abdominal wall resulted in more complete fistulas (Mellinger et al. 1991). Thus, it appears that correct stem length and tube sizing as well as stabilization of the device may be important for allowing timely tract maturation. When sizing the tube to the patient, care must be taken to avoid either a tight fit (which can lead to pressure necrosis) or a loose fit (which may lead to inadvertent tube removal or delayed tract maturation), while expecting and accommodating mild to moderate post-surgical swelling.

Metabolic Complications

Refeeding syndrome can occur during the provision of either enteral or parenteral nutrition. During starvation, homeostasis preserves extracellular concentrations of electrolytes, glucose, and other metabolic mediators despite whole body depletion. Refeeding syndrome occurs upon reintroduction of nutrients during this physiological state of starvation. Insulin is released in response to the sudden influx of carbohydrate, and a shift from the use of fatty acids and ketone bodies for energy. Insulin acts on peripheral cells to take up and utilize glucose, with subsequent increased intracellular movement and utilization of potassium, phosphorus, magnesium, and thiamin. The result is

hypokalemia, hypophosphatemia, hypomagnesemia, and relative thiamin deficiency.

Refeeding syndrome is a well-recognized problem in human medicine during the management of anorexia nervosa and other causes of malnutrition and starvation (Crook et al. 2001; Kraft et al. 2005). This problem can be serious and life threatening; however, even in the human medical literature, there is a dearth of published scientific investigation. Although many individual case reports have been published, prospective or retrospective studies of treatments, risk factors, and outcomes are lacking, especially in the context of critical illness. It appears that more severe consequences may occur in humans compared to animals, with profound water balance derangements, seizures, and cardiac failure frequently reported (Havala and Shronts 1990; Crook et al. 2001; Kraft et al. 2005). However, there are reports of apparent refeeding syndrome (hypophosphatemia and hemolytic anemia) in dogs that were fed with an enteral device after starvation (Silvis et al. 1980) and in cats provided with enteral nutrition support during the course of several different diseases (Justin and Hohenhaus 1995). A case report describes the management of a cat with refeeding syndrome (Armitage-Chan et al. 2006). It is unknown to what extent and for how long starvation must occur to elicit refeeding syndrome; however, it is likely to vary with individual animal factors. The extent of individual adaptation to the starvation state probably influences the manifestation of refeeding syndrome. It is likely to occur much sooner or with a higher rate of adverse consequences if the starvation was complete and prolonged rather than partial and brief. Additionally, patients that already have metabolic and hormonal derangements are likely at increased risk.

Local infection of the stomal site secondary to wound infection or due to constant drainage of food or gastric secretions can occur. Again, diligence in tube maintenance and monitoring is important for prevention and for early recognition of signs of infection. Severe problems such as abscessation or cellulitis may necessitate tube removal.

Gastrointestinal Complications

Tube placement can be associated with gastrointestinal complications. For example, there are concerns that nasoenteric tubes that must pass through the lower esophageal sphincter (LES), such as nasogastric and nasojejunal tubes, may lead to irritation and potentially reflux or aspiration. Several factors are likely responsible for increased reflux and aspiration risks; however, LES irritation does not appear to be a major cause of aspiration in humans, partly because tube size is not correlated with rates of aspiration (Gomes et al. 2003). A study in healthy dogs established that the use of size 14 French polyethylene esophagostomy tubes that terminated in the gastric lumen resulted in only minor complications (small abscess formation) in 3 out of 14 dogs, with no reports of reflux or aspiration (Cavalcanti et al. 2005). However, one study involving the use of pharyngostomy tubes that terminated in the gastric lumen reported complications that included mucosal erosions of the caudal esophagus and vomiting that resolved when the tube was repositioned (Crowe and Downs 1986). A study of healthy dogs with pharyngostomy tubes reported distal esophageal erosions and/or ulcerations in three out of six subjects; however, evidence of inflammation (perivascular lymphocyte infiltration) was noted in all but one dog (Lantz et al. 1983). Unfortunately the study was not only uncontrolled but also employed tubing made of irritating polyvinylchloride. It appears the presence of a tube into or traversing the pharynx may play a significant role in the occurrence of gastric reflux. In fact, a study in humans found that the presence of a catheter in the pharynx was adequate stimulation to cause a significant increase in the frequency of LES relaxation, suggesting that local stimulation of the pharyngeal area may be involved (Mittal et al. 1992). Further, stimulation of mechanoreceptors due to distension of the stomach causes relaxation of the lower esophageal sphincter in both dogs and humans (Franzi et al. 1990; Allocca et al. 2002; Penagini et al. 2004). This implies that simply feeding a patient may increase the risk of gastric reflux.

Esophagostomy tubes can also be positioned so that the termination is in the gastric lumen. A small controlled study in healthy dogs investigated the effects of two cervical esophagostomy tubing types (silicon and polyethylene) and two levels of tube termination (gastric lumen and mid-esophagus) on radiographic evidence of reflux and on gross and histopathological features on the esophagus and stomach (Balkany et al. 1977). The study found no effect of tubing material or length on contrast fluoroscopic evaluation. Also, abnormalities of the esophageal and/or gastric mucosa were most pronounced in the long polyethylene tube group (severe ulcerative esophagitis in three out of four dogs) and absent in the short polyethylene tube group (zero out of two dogs); however, excessive granulation tissue was noted at the mucosal stoma site of four of six dogs with polyethylene tubes. For dogs with silicon tubes, inflammation was noted at the distal esophagus in two of two dogs with long tubes and two of four dogs with short tubes. Overall, five of six dogs with tubes that terminated in the gastric lumen showed evidence of adverse effects

secondary to gastric reflux compared to two of six dogs with tubes that terminated in the esophagus. However, even dogs with short silicon tubes showed evidence of reflux. Also, tube sizes were not reported. Interpretation of the data from this small study is difficult, and it is clear that more definitive investigations are needed.

It is clear that multiple factors may be involved in LES competence, and the role enteral feeding devices may play is far from obvious. Also, placing a nasoenteric tube such that it terminates in the gastric lumen rather than in the distal esophagus allows for not only confirmation of correct placement with radiography, but also facilitates the evaluation of gastric residuals and the relief of gastric gas distension (Crowe 1986). However, in patients with normal esophageal function, there are no disadvantages to terminating the tube in the distal esophagus, and until further investigations have been done, clinical judgment and experience will suffice as guidance for the management of individual patients.

Enteral feeding intolerance can be manifested as a gastrointestinal complication. There have been reports of intolerance of early enteral feeding in people, including functional obstructions and delayed gastric emptying (Dedes et al. 2006; Nguyen et al. 2007). Although caution should also be exercised when feeding a patient with suspected severe gastrointestinal malfunction (such as severe ileus or malabsorption), evidence from the human literature indicates that early enteral feeding can facilitate a faster return of intestinal motility following gastrointestinal surgery (Ng and Neill 2006). A study of dogs with hemorrhagic gastroenteritis of unknown etiology reported increased survival in patients administered both parenteral and enteral nutrition compared to those provided only parenteral nutritional support, although vomiting was a severe problem in the former group (Will et al. 2005). In any case, signs of gastrointestinal intolerance (i.e., vomiting, diarrhea, or discomfort with feeding) are unpleasant for both the patient and staff and indicate that the administration volume and rate should be decreased.

The prevalence of vomiting and diarrhea in enterally fed veterinary patients is unknown, but it is believed to be high and of considerable consequence (Marks 1998). It is important to consider that many diseases will cause these clinical signs independent of enteral feeding, and patients with such clinical signs are likely to require nutritional support. However, feeding with an enteral device can predispose a patient to vomiting and/or diarrhea if the feeding is too fast, overly voluminous, or if the diet selected is inappropriate (i.e., high osmolarity, high fat). Food aversions can develop if patients experience nausea and vomiting associated with feeding specific diets. Management of enterally fed patients should include consideration of both rate and volume of food for either bolus or continuous rate infusion methods. Care should be taken to select appropriate diets for the disease process, and evaluation of the diet characteristics is indicated if intolerance is noted. For instance, diets high in fat will slow the rate of gastric emptying; a lower-fat formulation may be necessary if high volumes of gastric residuals are noted. Higher-fat diets should also be used cautiously in animals with malabsorptive diseases as clinical experience has shown that many cases can only tolerate restricted-fat diets. If enteral feeding intolerance is severe enough to impair recovery of the patient or is causing additional problems (e.g., electrolyte and fluid imbalances, further weight loss), the use of parenteral nutrition should be considered as a complementary modality or as the sole source of nutritional support.

TRANSITIONING PATIENTS TO VOLUNTARY INTAKE

While some patients will require feedings through enteral devices on a long-term and even lifelong basis (such as those with severe and permanent orofacial or esophageal disease or with chronic kidney disease), others need tubes only temporarily. As underlying conditions improve or resolve with time and medical management, appetite may be restored and interest in food will resume. At this point, the patient can be offered the diet before scheduled feedings when they should be hungry. If some or all of the diet is not consumed voluntarily, it can be administered through the tube. Transitioning away from tube feeding is often successful with this strategy, and is beneficial when the enteral diet incorporates strategies specific to the patient, such as a low-fat novel home-cooked diet slurry for animals with adverse food reaction and pancreatitis.

Other patients will have alternative options for longer-term diets, as there are many products with similar nutritional profiles appropriate for a variety of conditions. In these cases, a different diet than the one routinely fed through the tube may be accepted voluntarily, especially if food aversion occurred. Of course, for many situations, the diet choice will be driven by the needs of the specific patient. For instance, animals with fiber-responsive diarrhea, chronic pancreatitis, adverse food reactions, or other conditions will require diets with specific modifications. Ultimately, options for long-term diets and transition to voluntary intake will vary according to the underlying conditions and is dependent on the individual patient.

SUMMARY

- Hospitalized patients as well as those with trauma or chronic diseases are often malnourished or are consuming inadequate diets.
- Unless contraindicated, feeding enterally is preferred in order to provide energy and nutrients that support the function of the gastrointestinal tract.
- Enteral feeding devices are excellent options for providing adequate amounts of appropriate diets to patients with a wide range of needs.
- Enteral feeding devices can be readily and inexpensively utilized in any practice setting.

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Parenteral Nutrition

21

Sally C. Perea

INTRODUCTION

There is an increasing awareness among veterinarians of the importance of nutritional support in hospitalized patients. However, a recent study evaluating nutritional delivery to hospitalized dogs showed that we are still not adequately meeting the needs of our patients (Remillard, Darden et al. 2001). In this study, the caloric intakes and outcomes of 276 dogs over 821 days of hospitalization at four veterinary referral hospitals were retrospectively evaluated. Their findings revealed that caloric intake had a significant positive effect on patient outcome. However, the dogs in this study were also shown to be in a negative energy balance during the majority of the time of hospitalization (73% of the total days). Refusal to voluntarily eat orally accounted for 42% of the dogs that received inadequate energy during hospitalization. Generally, the first line of assisted feeding in anorectic patients is via the enteral route (Finck 2000). For patients in which enteral feeding is not tolerated, parenteral nutrition (PN) can be an essential tool to deliver nutritional needs.

HISTORY

Blood transfusions can be considered one of the first forms of PN, and they were reported experimentally in dogs as early as 1667 (Levenson et al. 1984). In 1873, when blood was unavailable, a physician by the name of Dr. E.M. Hodder took a bold step with one of the first reported uses of milk for intravenous infusion in a human patient with Asiatic cholera (Hodder 1873). This patient's condition was considered to be end-stage and fatal, giving Hodder the opportunity to try his experimental therapy. While his colleges did not support his pursuit (three of four were reported to have left the building), the patient tolerated the treatment and went on to recover.

Over time, the various components of current PN admixtures were introduced. Protein hydrolysates and glucose mixtures where reported to have been used intravenously as early as 1889 and 1896, respectively (Levenson et al. 1984). One of the first reports of intravenous injection of a fat emulsion was in 1915, when a 3% emulsion of lard was administered to two dogs (Levenson et al. 1984). Metabolic utilization of the fat was verified with a decrease in the respiratory quotient from 0.85 to 0.73, and a concurrent rise in heat production. The use of these various components were refined over time, and eventually combined to provide a three-in-one PN admixture providing all three of the major macronutrients.

The dog was used as an experimental model in many of these early studies and was the subject in one groundbreaking study that used PN as the sole nutrient source for normal growth in six 12-week-old Beagle puppies for up to 256 days (Dedrick, Wilmore, Vars et al. 1968). The use of PN in veterinary patients did not emerge until much later and is still in its early stages in regard to available randomized case-controlled prospective clinical studies. Our current knowledge of PN in dogs and cats is mainly limited to healthy animal research studies, retrospective clinical reports, clinical experience, and extrapolation from human literature.

Applied Veterinary Clinical Nutrition, First Edition. Edited by Andrea J. Fascetti, Sean J. Delaney.

ASSESSMENT OF NUTRITIONAL STATUS AND PATIENT SELECTION

The first criterion to consider when evaluating a candidate for PN is the patient's nutritional status. One of the most important tools for determining a patient's nutritional status is a thorough diet history. It is important to determine not only the length of complete anorexia, but also the length of inadequate nutritional intake. To assess for adequate intake, the current energy intake should be quantified and compared to the patient's calculated energy requirement. It is also important to inquire both about the feeding of commercial pet foods and human or home-cooked foods. Animals that consume unbalanced home-cooked foods and human foods from the table may have an increased risk of nutrient deficiencies and imbalances.

In addition to diet history, other components of the history, including presence of vomiting, diarrhea, and underlying disease should be considered. Vomiting and diarrhea reflect the presence of maldigestion, malabsorption, and the loss of essential nutrients (i.e., protein, fat, and electrolytes) via the gastrointestinal tract. Other conditions that result in excess protein loss, such as open abdomen or large wounds or burns also negatively impact nutritional status. Finally, many metabolic diseases negatively impact nutritional status, particularly chronic diseases that can lead to anorexia and cachexia such as chronic renal disease and congestive heart failure.

The next important tool for assessment of a patient's nutritional status is the physical exam. Body weight, body condition score, and muscle mass should be assessed in all patients. Change in body weight is often more insightful than the patient's current body weight, as many patients may appear to have a healthy body weight and body condition, but have undergone unintentional weight loss. A history of weight loss at presentation has been shown to double the risk of mortality in feline PN patients (Pyle et al. 2004). Any unintentional weight loss is a concern, but weight loss greater than 2% of the body weight per week is considered severe (Remillard 2000). Assessment of muscle mass is also an important component of the physical exam. Muscle wasting commonly occurs secondary to hypercatabolism in critically ill patients and may be present in patients who appear to have a normal body condition score (Michel, King et al. 1997; Chan 2004). A 3-point muscle condition scoring system has been described, with 3 out of 3 being normal muscle mass, and 1 out of 3 representing severe muscle wasting (Buffington et al. 2004). Assessment of muscle mass should be made by palpation over the temporal bones, ribs, lumbar vertebrae, and pelvic bone, and visual assessment of bony prominences from a distance.

Finally, some hematological markers can be helpful when assessing nutritional status. Although not specific, changes in serum concentrations of albumin, potassium, and red blood cell and lymphocyte counts can reflect nutritional status (Fascetti et al. 1997; Remillard 2000; Freeman and Chan 2006). Serum potassium concentrations reflect changes on a day-to-day basis, while albumin, red blood cell, and hemoglobin concentrations reflect changes in nutritional status over weeks to months. Although albumin is one of the main hematological markers referenced to assess nutritional status, its concentration is dependent on a number of variables (including body water status, liver function, and renal losses), making it an unspecific marker. However, in human medicine albumin concentration has been demonstrated to correspond to overall health status and mortality rate (DeLegge and Drake 2007). Albumin concentration has also been shown to correlate with mortality rate in feline patients prior to and 96 hours after starting PN support (Pyle et al. 2004). Therefore, while albumin concentration may not always directly correspond to nutritional status, it can be a useful prognostic indicator in critically ill patients (Mehl et al. 2005).

After assessing the patient's history, physical exam, and hematological status, consideration must also be given to the expected course of the patient's illness. For those patients with acute injuries (e.g., hit by car) or elective surgeries, and their nutritional status at presentation is generally good, the period of withholding of food and/or anorexia is expected to be short (1 to 3 days). For these patients, voluntary intake is expected to resume within a short time period, and it is reasonable to delay nutritional support. However, animals with chronic illnesses are more likely to have a poor nutritional status at presentation and may have an extended period where voluntarily food intake is expected to be reduced or absent. For these patients, nutritional support should be implemented as soon as possible.

Unlike in human medicine, standardized illness scores and specific guidelines for implementation of assisted feeding have not been established for veterinary patients. Table 21.1 provides a list of considerations that can serve as a guideline for assigning patients into categories of low, moderate, or high risk for malnutrition. This list is by no means exhaustive, but can serve as a starting place for clinicians in the decision making process. Each patient should be assessed, taking into consideration the wide range of individual variables, rather than setting an arbitrary cutoff point for when assisted feeding should be

Table 21.1. Nutritional Assessment Guidelines

	Low Risk	Moderate Risk	High Risk
History			
Intake < RER for < 3 days	√		
Intake < RER for 3–5 days		√	
Intake < RER for > 5 days			√
Anorexia < 3 days		√	
Anorexia > 3 days			√
Weight Loss			√
Vomiting/Diarrhea*		√	√
Other factors (may be low, moderate, or high risk)			
Physical Exam			
BCS < 4/9			√
Muscle wasting present			√
Other factors (may be low, moderate, or high risk)			
Hematological Parameters			
Hypoalbuminemia*		√	√
Electrolyte abnormalities*		√	√
Anemia*		√	√
Lymphopenia*		√	√
Expected Course of Illness			
< 2 days	√		
2–3 days		√	
> 3 days			√

Patients with two or more high-risk factors should receive nutritional support as soon as they are appropriately stabilized. Patients with two or fewer moderate-risk factors should be carefully monitored, and assisted feeding should be implemented within two to three days of hospitalization if the condition does not significantly improve. Patients with only low-risk factors should also be carefully monitored to ensure that their nutritional status does not decline during hospitalization.

*The degree of clinical signs and hematological abnormalities will dictate moderate- to high-risk assignment.

implemented. When a patient has two or more high-risk factors for malnutrition, it is likely that that the patient is already in a malnourished state, and assisted feeding should be implemented as soon as possible (cardiovascular and electrolyte stability is a priority and must be established prior to nutritional intervention). Cats with hepatic lipidosis or at risk for hepatic lipidosis should also receive prompt nutritional support. Patients with two or more moderate-risk factors should be carefully monitored, and assisted feeding should be implemented within 2 to 3 days of hospitalization if the condition does not significantly improve. Patients with only low-risk factors should also be carefully monitored to ensure that their nutritional status does not decline during hospitalization.

Following the nutritional assessment of the patient, the decision must then be made as to what route of nutritional support is the most appropriate for the patient. In general, enteral nutrition is preferred over PN when the gastrointestinal tract is functional (see Fig. 21.1). Indications for PN include intractable vomiting and/or diarrhea; anesthesia or lack of a gag reflex; recovery from severe gastric or intestinal resection; poor anesthetic candidate for proper feeding tube placement; or inability to meet full energy requirements via enteral route. Patients with severe

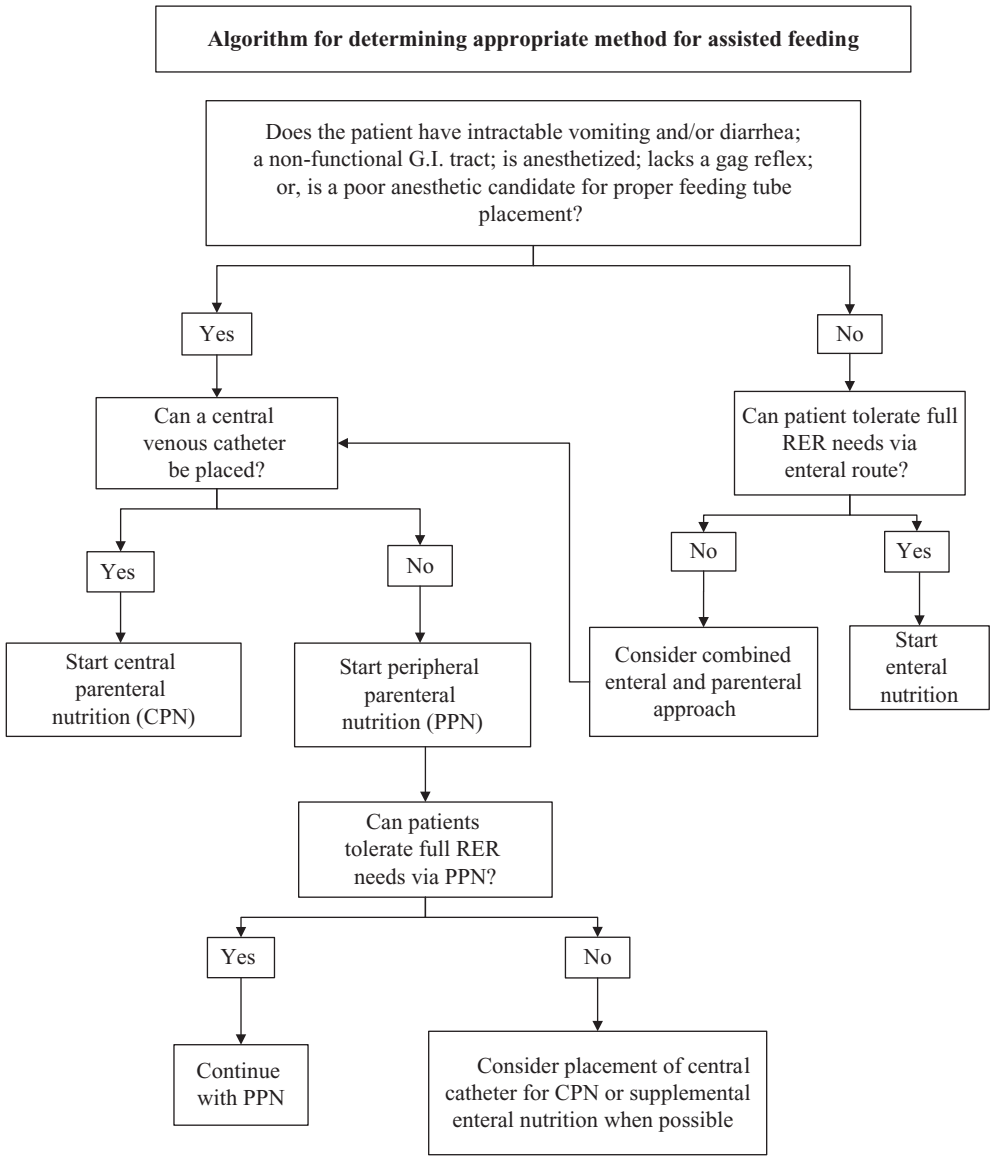

Fig. 21.1. Algorithm for determining the appropriate method for assisted feeding.

chylothorax are also candidates for PN, as parenteral administration of lipids bypasses the lymphatic system and thoracic duct (Suddaby and Schiller 2004). Successful reduction in triglyceride content of effusion from 1188 mg/dL to 29 mg/dL has been reported with PN treatment in one veterinary chylothorax patient (Lippert, Fulton et al. 1993).

The most commonly reported disease state in veterinary patients that require PN is pancreatitis (Chan, Freeman, Rozanski et al. 2006; Pyle et al. 2004; Lippert, Fulton, and Parr 1993) followed by gastrointestinal (Reuter, Marks, Rogers, and Farver 1998) and hepatic diseases/hepatic lipidosis (Crabb et al. 2006). Although enteral feeding via jejunostomy tube is the preferred feeding method in patients with pancreatitis, patients that are not surgical candidates for placement of jejunostomy tubes are often selected for PN. For a complete discussion on enteral feeding, please see Chapter 20 on enteral nutrition.

NOMENCLATURE

PN can be classified by the route of administration (central or peripheral) or by the degree of nutrition provided (total or partial). The term "total parenteral nutrition" (TPN) implies that the patient's complete nutritional needs are provided by the parenteral solution, which is not common practice in short-term (days to weeks) parenteral solutions administered to veterinary patients. The average duration on PN in dogs and cats from five comprehensive retrospective studies is 3.89 days, with a range of 0.3 to 25 days (Lippert, Fulton et al. 1993; Reuter et al. 1998; Chan, Freeman, Labato et al. 2002; Pyle et al. 2004; Crabb et al. 2006). PN solutions used in veterinary medicine do not commonly provide all of the essential minerals and fat-soluble vitamins and are, therefore, not truly TPN solutions. Some define TPN as providing total energy needs, while partial parenteral nutrition provides only partial energy needs. Using this definition, TPN solutions are generally administered centrally, while partial parenteral solutions are generally administered peripherally. However, it is possible to administer complete energy needs peripherally when utilizing high-fat solutions, while it can also be common practice to administer only partial energy needs centrally. Because of the discrepancies in nomenclature, this discussion will use the terms "central parenteral nutrition" (CPN) and "peripheral parenteral nutrition (PPN)," focusing on the characteristics of the solution that determine the route of administration.

DETERMINATION OF ADMINISTRATION ROUTE

PN may be administered via central or peripheral venous access. While peripheral venous access is easier to establish, central venous access provides more flexibility in the formulation of the parenteral solution. The primary limitation of peripheral solutions is the lower osmolarity that is required to prevent thrombophlebitis. Recommendations for maximum osmolarity of peripheral solutions range from 600 to 750 mOsmol/L, while central solutions can be as high as 1,400 mOsmol/L (Delaney et al. 2006; Campbell et al. 2006). Based on the author's clinical experience, the more conservative end of this range is preferred for peripheral solutions, especially in patients with hypercoagulable conditions. To achieve this reduced osmolarity, the parenteral solution must be formulated with a less concentrated dextrose solution, which decreases the energy density of the final solution. To help offset this effect, the calories provided by fat can be increased. Lipid solutions have a low osmolarity and high energy density, and therefore help to reduce the osmolarity and increase the energy density of the final solution. Most patients can tolerate these higher-fat solutions (Remillard 2000); however, those with preexisting hyperlipidemia or who develop hyperlipidemia while on parenteral nutrition may require CPN to deliver complete energy needs.

When central venous access is obtainable, CPN is generally preferred due to fewer restrictions in solution formulation, easier ability to meet full energy requirements, and reduced incidence of thrombophlebitis. However, successful administration of PPN in dogs and cats has been described (Chan, Freeman Rozanski et al. 2006; Zsombor-Murray and Freeman 1999) and may be a more practical tool for practitioners who do not routinely place central catheters. Shorter durations of PN administration and the use of lipid-containing admixtures can also help to reduce the incidence of thrombophlebitis (Chandler, Guilford et al. 2000; Chandler and Payne-James 2006). In larger patients with neck injuries, or any size patient with coagulopathies, peripheral catheters may be required or preferred, therefore making PPN the method of choice for nutritional support.

Independent of the route of PN elected, it is important to continually reevaluate the patient and consider introduction of enteral nutrition. Although most patients who are initially started on PN are not candidates for enteral nutrition, many may tolerate a slow weaning onto enteral nutrition or a proportion of their energy and nutrient needs simultaneously administered by the enteral route (Griffiths and Bongers 2005). This concurrent implementation of enteral feeding may help to maintain intestinal integrity as well as immune and gut-barrier functions (Heidegger et al. 2007), while still providing adequate energy and meeting nutrient needs via the combined parenteral approach. One retrospective study evaluating partial PN in dogs and cats demonstrated improved survival in patients receiving concurrent enteral nutrition (Chan, Freeman, Labato et al. 2002), providing further support for a combined approach.

CATHETER SELECTION AND PLACEMENT

Appropriate selection and management of peripheral catheters can help to minimize the risk of thrombophlebitis. Teflon catheters are associated with a high incidence of thrombophlebitis, while thrombophlebitis is reduced with the use of silicone and polyurethane catheters (Reynolds et al. 1995). Polyurethane catheters have a higher internal gauge with the same external diameter when compared to silicone catheters and have been shown to result in fewer occlusions (Culebras et al. 2004; Plusa et al. 1998). The use of small diameter catheters, proper catheter care, and

Fig. 21.2. Placement of a multi-lumen polyurethane catheter in a dog for CPN administration.

frequent catheter replacement can also reduce the incidence of thrombophlebitis (Chandler, Guilford et al. 2000).

Multi-lumen polyurethane catheters are commonly utilized for CPN administration (Fig. 21.2). Multi-lumen catheters provide the advantage of having a dedicated port for PN administration, with additional ports for blood draws, and crystalloid fluid and drug administration. These catheters are available in a wide range of diameters (4.5–8.5 Fr.) and lengths (8–60 cm) (Arrow International, Inc. Reading, PA). The shorter lengths are generally used for jugular placement, while the longer catheters can be used for peripherally inserted central venous catheters (centrally placed via the medial saphenous vein). Central placement can be radiographically verified and is highly recommended for peripherally inserted central venous catheters. In humans, peripherally inserted central venous catheters have been associated with higher rates of thrombophlebitis (Cowl et al. 2000). Although this has not been evaluated in dogs and cats, it is the author's clinical experience that complications associated with thrombophlebitis are more commonly seen with peripherally inserted central venous catheters. Because of this, jugular placement of central venous catheters is preferred when possible.

PARENTERAL NUTRITION COMPONENTS

Protein

Protein needs in PN are provided by amino acid solutions, which are available in 8.5% and 10% concentrations. Until recently, amino acid solutions could be purchased with or without added electrolytes; however, many electrolyte-containing solutions are being phased out and will no longer be available. The most commonly utilized amino acid solutions have a concentration of 8.5%, with an energy density of 0.34 kcal/ml and osmolarity of 706–880 mOsmol/L. Therefore, compared to the lipid and dextrose components, the amino acid solution contributes a relatively low energy density, a moderately high osmolarity (Table 21.2).

Because parenterally administered amino acids are essentially 100% bioavailable, protein requirements that are established for oral feeding of commercial pet foods likely overestimate needs for parenteral administration. A nitrogen balance study conducted in healthy dogs while receiving PN evaluated protein levels of 0, 1.36, or 2.04 g amino acid/kg body weight over a 7-day period (Mauldin et al. 2001). One group received crystalloid fluids only, and the remaining three groups received one of the above protein levels with the remaining of their maintenance energy requirements (MERs) provided by 50% lipid and 50% dextrose on a caloric basis. They demonstrated that administration of MER needs from carbohydrate and fat had a protein-sparing effect, with a greater negative nitrogen balance in dogs administered only crystalloid fluids compared to those administered the protein-free lipid and dextrose solution. All dogs where shown to be in a negative nitrogen balance, and calculations based on a linear relationship between nitrogen balance and amino acid administration estimated a requirement of 2.3 g protein/kg/d to achieve nitrogen balance. The dogs in this study averaged approximately 10 kg in body weight, with a calculated MER of 766 kcal/day. Therefore, this minimum protein requirement is equivalent to 3.0 g/100 kcal (12% protein on a metabolizable energy basis). This level is lower than requirements established by the Association of American Feed Control Officials (AAFCO) for adult canine maintenance (5.14 g/100 kcal) for commercial pet foods but slightly greater than the minimum recommended allowance established by the National Research Council (NRC) for adult canine maintenance (2.5 g/100 kcal).

The protein requirements in critically ill animals are likely different from healthy animals, as elevations in endogenous corticosteroids, catecholamines, and inflammatory cytokines promote a hypercatabolic state (Chan 2004). An evaluation of urinary nitrogen excretion in critically ill dogs demonstrated losses that are two to six times the obligatory nitrogen excretion that is reported in healthy dogs (Michel, King et al. 1997). A healthy animal under conditions of starvation will adapt by decreasing muscle breakdown, converting primarily to the use of fatty acids and ketones for energy. However, in critically ill patients, muscle catabolism is not appropriately downregulated. In ill animals, the amino acids generated from muscle break-

Table 21.2. Commonly Used Solutions and Supplements for Parenteral Nutrition

Ingredient	Energy Density & Key Nutrient Contents	Osmolarity
Amino Acid Solutions		
Travasol 8.5%*	0.34 kcal/ml	880 mOsmol/L
Travasol 10%*	0.4 kcal/ml	998 mOsmol/L
Aminosyn II 8.5%†	0.34 kcal/ml	706 mOsmol/L
Lipid Solutions		
Intralipid 10%*	1.1 kcal/ml 0.015 mmol PO_4/ml	260 mOsmol/L
Intralipid 20%*	2 kcal/ml 0.015 mmol PO_4/ml	260 mOsmol/L
Liposyn II 10%†	1.1 kcal/ml	276 mOsmol/L
Liposyn II 20%†	2 kcal/ml	258 mOsmol/L
Dextrose Solutions		
Dextrose 5%	0.17 kcal/ml	253 mOsmol/L
Dextrose 50%	1.7 kcal/ml	2,525 mOsmol/L
Dextrose 70%	2.38 kcal/ ml	3,640 mOsmol/L
Electrolytes		
Potassium chloride	2 mEq K/ml	4,000 mOsmol/L
Potassium phosphate	4.4 mEq K/ml 3 mmol PO_4/ml	7,357 mOsmol/L
Magnesium sulfate 50%	4.06 mEq Mg/ml	4,060 mOsmol/L
Sodium chloride 23.4%	4 mEq Na/ml	8,000 mOsmol/L
Sodium chloride 14.6%	2.5 mEq Na/ml	5,000 mOsmol/L
Vitamins & Minerals		
Vitamin B complex**	Thiamine – 12.5 mg/ml Niacin – 12.5 mg/ml Pyridoxine – 5.0 mg/ml Pantothenic acid – 5.0 mg/ml Riboflavin – 2.0 mg/ml Cyanocobalamin – 5.0 mcg/ml	382.5 mOsmol/L

*Baxter Healthcare Corporation, Clintec Nutrition Division, Deerfield, IL, 60015, USA.
†Hospira Worldwide Inc., Lake Forest, IL 60045, USA.
**Vedco, Inc., 5503 Corporate Dr., St. Joseph, MO 64507, USA.

down are primarily used for gluconeogenesis and production of acute phase proteins, while synthesis of other selected proteins (such as albumin, transferrin, prealbumin, retinol-binding protein, and fibronectin) is actually decreased (Biolo et al. 1997).

The standard recommendations for protein levels in PN formulations is 4–5 g/100 kcal (16–20% protein on an ME basis) for dogs and 6 g/100 kcal (24% protein on an ME basis) for cats (Freeman and Chan 2006). The goal of PN support should be providing adequate amounts of protein to minimize muscle breakdown and maintain lean body mass. Like energy, excessive protein should be avoided, as attempts to promote tissue anabolism through high-energy/high-protein PN administration have lead to complications such as azotemia and cholestasis (Klein et al. 1998). The level of protein included in PN solutions is also dependent on individual patient needs and disease states. Animals with renal disease and hepatic

encephalopathy should be provided with reduced protein levels, while growing animals and patients with significant protein losses may require increased protein levels.

Fat

Fat, provided by lipid emulsions, is an important component of PN, supplying both energy and essential fatty acids. The most commonly utilized lipid emulsion is a 20% solution, providing 2 kcal/ml with an osmolarity of 260 mOsmol/L. The lipid component of PN provides beneficial qualities to the final admixture, helping to balance out the high osmolarity of the dextrose solution while boosting the overall energy density. Recommended fat levels in PN formulations range from 30% to 80% of total calories (Remillard 2000; Freeman and Chan 2006; Delaney et al. 2006). Higher fat levels (60–90% of nonprotein calories) have been reported to be well tolerated clinically in over 500 patients over a 5-year period (Remillard 2000). Because animals that have been without food for over 3 days are utilizing primarily endogenous fat for energy, these higher-fat solutions may be more physiologically appropriate. Lower fat levels may be needed in animals with preexisting hyperlipidemia, or who develop persistent lipemia while on PN. Although fat restriction is recommended for oral feeding in patients with pancreatitis, intravenous fat does not stimulate exocrine pancreatic secretion (Fried et al. 1982; Stabile et al. 1984); therefore, fat restriction is not necessary in PN formulations for patients with pancreatitis.

Lipid emulsions available within the United States are generally soybean oil and/or safflower oil based with additional egg yolk phospholipids, glycerin, and water. Elimination and long-term (91-day) administration studies of lipid emulsions have been conducted in dogs (Cotter, Martis, Cosmas et al. 1984; Izzo, Larcker, Remis et al. 1984). No significant differences in the maximum elimination capacity or fractional elimination rates of 10% Intralipid at bolus injection doses of 300 g/kg body weight or with continuous infusion doses of 3 or 6 g/kg body weight were found, indicating that the elimination mechanism had not been saturated. The researchers did, however, note that some of the data did not fit their model at the 6 g/kg level, suggesting individual variability in the ability to handle the lipid at higher administration rates. This finding reflects what is seen clinically, with some patients requiring reduced fat levels due to persistent hyperlipidemia during PN administration.

Soybean and safflower oil-based emulsions are composed of primarily omega-6 fatty acids and have been shown to inhibit lymphocyte proliferation and neutrophil chemotaxis and migration (Granato et al. 2000). These suppressive effects on the granulocyte and reticuloendothelial cell systems have raised concerns of immunosuppressive effects of high-lipid-containing PN solutions. The clinical significance of these effects is unknown and has yet to be evaluated in the dog and cat. The use of fish oil, olive oil, and medium-chain triglyceride based fat emulsions have been shown to reduce or eliminate these negative immunosuppressive effects (Chao et al. 2000; Wanten and Calder 2007; Sala-Vila et al. 2007). Use of these lipid sources in dogs and cats may prove beneficial; however, they are currently unavailable in the United States.

CARBOHYDRATE

Dextrose solutions, ranging in concentrations from 5% to 70% are utilized in PN solutions to provide carbohydrate calories. Fifty-percent dextrose is one of the most commonly used concentrations for CPN formulation, providing 1.7 kcal/ml, with an osmolarity of 2,525 mOsmol/L. For PPN formulations, 5% dextrose is commonly substituted, providing a tenfold lower osmolarity of 253 mOsmol/L, and an energy density of 0.17 mOsmol/L. Alternatively, some institutions or compounding pharmacies may utilize a higher dextrose solution and sterile water for peripheral PN formulations, titrating to an appropriate osmolarity for peripheral venous administration.

Recommended carbohydrate levels for PN solutions range from 20% to 50% on a ME basis (Delaney et al. 2006). Levels as high as 62% of the total calories have been well tolerated in healthy dogs over a 9-day period, although moderate hyperglycemia was present during the early days of administration (Zentek et al. 2003). In order to avoid complications associated with hyperglycemia, some have recommended that rates of administration should not exceed 4 mg/kg/min (Freeman and Chan 2006). This rate is extrapolated from human data, where rates exceeding this level resulted in hyperglycemia in nondiabetic patients. Dextrose provides 0.034 kcal/mg; therefore, 4 mg/kg/min is equivalent to 0.136 kcal from dextrose/min/kg. For a 10-kg animal receiving RER (393 kcal/day) over a 24-hour period, total kcal/min administration would be approximately 0.03 kcal/kg/min. Since only a portion of the total energy is provided by dextrose, these maximum dextrose infusion rates are not typically reached during routine PN administration. However, hyperglycemia is the most common metabolic complications seen with PN administration in dogs and cats (Lippert, Fulton et al. 1993; Reuter et al. 1998; Chan, Freeman, Labato et al. 2002; Pyle et al. 2004; Crabb et al. 2006); therefore, avoiding high concentrations of dextrose is recommended. Higher levels

are sometimes unavoidable in patients that require protein and/or fat restriction for other disease conditions. Lower levels may be beneficial in diabetic patients and animals that develop persistent hyperglycemia during PN administration. While dogs appear to adapt to high dextrose infusions after 1 to 2 days of PN administration (Reuter et al. 1998; Zentek et al. 2003), cats have been reported to have persistent hyperglycemia after 3 days of PN administration (Pyle et al. 2004). Therefore, lower carbohydrate formulations may be more appropriate for cats.

Electrolytes and Trace Minerals

Potassium and phosphorus are the most commonly added electrolytes to PN admixtures for dogs and cats. Hypokalemia and hypophosphatemia can occur with refeeding syndrome and are routinely added to PN solutions (see discussion under complications). For patients that are normokalemic, potassium phosphate should be added to provide 20 to 30 mEq K^+/L (Remillard 2000). Phosphorus is commonly provided by both the lipid solution and the additional potassium phosphate solution. Although no specific guidelines have been published for phosphorus content of canine and feline PN solutions, recommendations for human PN solutions range from 20 to 40 mM/L (Mirtallo 2001). For patients with preexisting hyperphosphatemia and/or hyperkalemia (such as commonly seen in patients with renal disease), potassium chloride can be substituted or omitted. It is recommended that any additional electrolyte abnormalities be corrected through crystalloid fluid supplementation, as the risk of solution instability and mineral precipitation is greater with additions to PN admixtures. Additionally, if reduced concentrations of electrolytes are required after the additions have been made to crystalloid fluids, the cost of replacement is significantly less than replacement of the PN solution.

Recommendations for the addition of trace minerals to PN admixtures in veterinary medicine are highly variable. Some institutions do not routinely include trace minerals (Pyle et al. 2004), while other institutions add four trace minerals (chromium, copper, manganese, and zinc) based on clinician preference (Crabb et al. 2006), or routinely add zinc only (Michel 2007). It has been the author's clinical experience not to include trace minerals to PN admixtures due the relatively short time period in which veterinary patients are receiving PN and the low likelihood that a nutrient deficiency will develop. For patients on PN for longer than 2 weeks, the addition of trace minerals should be considered.

When adding electrolytes and/or trace minerals to PN admixtures, it is important to recognize the potential risks of instability and precipitation within the solution. Mineral stability within the nutrient admixture can vary based on the form used, pH of the solution, ambient temperature, and the concentrations of amino acids, dextrose, and other electrolytes within the solution (Allwood and Kearney 1998). In general, monovalent ions are stable within PN admixtures, while di- and trivalent ions are more likely to form insoluble complexes. The most commonly reported precipitate within PN admixtures is calcium phosphate (Allwood and Kearney 1998). This has primarily been a problem in human infant PN admixtures, which require higher concentrations of calcium and phosphorus than adult formulations (Parikh et al. 2005).

There is little information about the stability of trace minerals within PN admixtures. Chromium, copper, manganese, and zinc have been shown to be both stable and compatible in PN admixtures for up to 48 hours at ambient temperature (Allwood and Kearney 1998). However, formation of copper and iron precipitates has been reported within solutions containing sulfur amino acids (Hardy et al. 1998; Allwood, Martin et al. 1998). Precipitates can be difficult to visualize due to the opaque nature of the lipid-containing PN solutions. The use of inline filters can help to provide protection from precipitates that are not grossly visible.

Vitamins

Because of their relatively rapid turnover rates and essential roles as cofactors in energy metabolism, B vitamins are important components of the PN solution. Most veterinary commercial B-vitamin complexes contain thiamin, niacin, pyridoxine, pantothenic acid, riboflavin, and cyanocobalamin. Folic acid is not compatible with riboflavin and is, therefore, not included in B-complex solutions. Cobalamin (vitamin B12) is generally the limiting B vitamin in terms of the amount needed to achieve minimum nutrient requirements. The amount added to the PN solution should be sufficient to meet established nutrient requirements (see Worksheet 21.1).

Because of their relatively slow turnover rates, fat-soluble vitamins are not routinely added to PN solutions for short-term administration in dogs and cats. For patients with specific nutrient concerns, such as vitamin K deficiency in patients with hepatic disease, parenteral formulations may be administered separately. Additionally, for patients with long-term fat malabsorption, it has been recommended to give a one-time intramuscular administration of a vitamin A, D, and E complex (Vital E-A+D, Schering-Plough Animal Health Crop., Kenilworth, NJ),

Worksheet 21.1. Step-by-Step Calculations for Parenteral Formulations

Step 1
kcal/day

Determine Energy Requirement
Resting Energy Requirement (RER) = 70 × (body weight in kg)$^{0.75}$

Step 2
Protein

Determine Macronutrient Volumes
_____% ME × ____ RER (kcal/day) = ____ $protein_{kcal}$
_____ $protein_{kcal}$ ÷ _____ kcal/ml amino acid solution
= _____ **ml amino acid solution**

Fat
_____% ME × ____ RER (kcal/day) = ____ fat_{kcal}
_____ fat_{kcal} ÷ _____ kcal/ml lipid solution
= _____ **ml lipid solution**

Carbohydrate
_____% ME × ____ RER (kcal/day) = ____ $carbohydrate_{kcal}$
_____ $carbohydrate_{kcal}$ ÷ _____ kcal/ml dextrose solution
= _____ **ml dextrose solution**

Step 3
Potassium level desired should be determined by patient's serum potassium concentration

Determine Volume of Potassium Supplement
mEq K^+ needed = ___mEq/L K^+ desired × ___total macronutrient volume/100
volume KPO_4 **=** ____mEq K^+ needed ÷ 4.4 mEq/ml = _____ **ml KPO_4**
OR, for patients with hyperphosphatemia, use potassium chloride:
Volume KCl = ____mEq K^+ needed ÷ 2 mEq/L = _____ **ml KCl**

Step 4
Check phosphorus level and add additional supplementation if needed

Calculate Total Phosphorus
____mls lipid solution × ____mmol P/ml = ____mmol phosphorus
____mls KPO4 × ____mmol P/ml = ____mmol phosphorus
_____total mmol phos

Step 5
Add B-vitamin complex at amount needed to meet the following requirements

Calculate Volume of Vitamin-B Complex
Thiamin – 0.29 mg/1000 kcal solution
Riboflavin – 0.63 mg/1000kcal solution
Niacin – 3.3 mg/1000 kcal solution
Pantothenic Acid – 2.9 mg/1000 kcal solution
Pyridoxine – 0.29 mg/1000 kcal solution
Cyanocobalamin – 6.0 mcg/1000 kcal solution

Step 6

Calculate Total Volume & Osmolarity
_____ mls amino acid solution × ____mOsm/ml = _____mOsmol
_____ mls lipid solution × ____mOsm/ml = _____mOsmol
_____ mls dextrose solution × ____mOsm/ml = _____mOsmol
_____ mls KCl or KPO4 × ____mOsm/ml = _____mOsmol
_____ mls B-vitamin complex × ____mOsm/ml = _____mOsmol
_____ total volume **_____total mOsmol**
Total mOsmol/L = total mOsmol/total volume

Step 7

Calculate Energy Density of Solution
Energy Density = ____total kcals (RER) ÷ ____ml total volume
= ____kcal/ml

that will provide the needed nutrients for up to 3 months (Remillard 2000).

ENERGY REQUIREMENTS

The goal of PN support is to provide an appropriate level of energy to sustain critical physiologic processes (such as immune function and wound healing) and maintain lean body mass, without overly stressing the patient's metabolic system with excessive nutrients. Many critically ill patients are underweight, and there is a tendency to desire weight gain in these animals. However, overfeeding is a common complication with PN and may contribute to problems such as cholestasis, hepatic lipidosis, and respiratory failure (Mauldin et al. 2001). Overfeeding may also contribute to hyperglycemia, which is a known negative prognostic indicator in critically ill human and feline patients receiving PN (Pyle et al. 2004; Cheung et al. 2005; Lin et al. 2007).

Energy needs can vary from patient to patient, and the ideal situation would be to measure individual patient needs via indirect calorimetry as is commonly utilized in human hospitals (Boullata et al. 2007). However, these measurements are costly and unavailable in most veterinary hospital settings; therefore, calculated requirements remain the most practical tool to estimate energy needs.

During hospitalization, patients are generally estimated to require energy levels equivalent to their calculated resting energy requirement (RER). There are multiple RER calculations that have been recommended, but exponential equations utilizing the patient's metabolic body weight are preferred. Linear equations are not recommended due to likely overestimation of true needs for small and larger animals. The use of illness energy factors are no longer recommended, as multiplying RER by these factors generally results in overestimation of true energy needs is hospitalized patients (O'Toole et al. 2004). Patients should be initially weaned onto RER, starting at approximately 25% of RER, followed by 25% increases every 8 to 12 hours until full RER is reached. Once full RER has been reached, the patient may be reassessed to determine if increased levels are needed. In the author's clinical experience, energy levels above RER are rarely needed, and maintaining more conservative rates helps to decrease metabolic complications associated with overfeeding.

It is the author's preference to include all nutrients (protein, fat, and carbohydrate) for energy calculations. There is mixed opinion among veterinary nutritionists whether protein calories should be accounted for in PN formulations. Some argue that protein needs should be met first, with the caloric needs met by fat and carbohydrate alone. Conversely, not accounting for protein calories has been argued as a potential cause for complications associated with overfeeding in veterinary patients receiving PN (Crabb et al. 2006). Additionally, one prospective study in healthy cats demonstrated detrimental effects on hepatic function in cats receiving PN doses that did not account for protein calories, while the same effect was not appreciated in the cats receiving PN doses that did account for protein calories (Lippert, Faulkner et al. 1989). However, all cats in this study received doses of 1.4 times their calculated RER, which could have also contributed to the complications seen with overfeeding. The calculations presented in this chapter will account for protein calories. Independent of the method used, the primary conclusion is that overfeeding should be avoided.

FORMULATION CALCULATIONS

Step-by-step calculations for PN formulations are outlined in Worksheet 21.1. The first step is to calculate the energy needs of the patient, using the calculation for RER. As mentioned above, illness energy factors are not recommended due to concerns of overfeeding. However, body weight should be monitored, and individual variations in energy needs should be considered after the patient has been weaned onto full RER. Steps 2 to 4 require selection of the desired energy distribution (percentage protein, percentage fat, and percentage carbohydrate on an ME basis) and electrolyte concentrations. These values will be determined on an individual patient basis as discussed above. Table 21.2 outlines the energy density of commonly utilized components to aid in these calculations. Step 5 requires the calculation of the needed volume of B-vitamin complex. The volume of B-vitamin complex required will vary based on the product used and should be provided in amounts necessary to meet the patient's established requirements. B vitamins have a wide margin of safety, so it is common practice to provide slightly higher volumes than needed to meet minimum requirements. This also provides a safety buffer for expected UV degradation. Finally, the total volume, osmolarity, and energy density of the solution are calculated in Steps 6 and 7.

COMPOUNDING

Because lipid-containing PN solutions are supportive of bacterial and fungal growth, preparation must be conducted with careful, aseptic techniques. Preparation within a laminar flow hood has been the minimum standard in recent years. However, the United States Pharmacopeia (USP) has established new guidelines for the preparation of sterile compounding that are becoming the new standard of care (Campbell et al. 2006). PN is classified as a

medium-risk formulation, and compounding should be conducted within an International Organization for Standardization (ISO) Class 5 environment (≤ 352,000 particles of 0.5 µm or larger size per m^3) such as a clean room or mobile isolation chamber. Although these new regulations are only enforced for the preparation of human PN formulations, it is prudent for veterinary medicine to strive to achieve the same quality of care.

The PN components may be mixed using manual or automatic methods. Manual compounding uses gravity flow of individual components, feeding into an empty sterile PN bag or glass bottle (Figs. 21.3 and 21.4). While the manual method does not require expensive automatic compounding equipment, it is slow, prone to inaccuracies, requires multiple manipulations, and has an increased likelihood of contamination (Mirtallo 2001). Automated compounding devices help to eliminate these increased risks of human error and contamination but are more expensive and may not be available in some areas (Figs. 21.5 to 21.7).

For either method of compounding, it is important to ensure that appropriate mixing procedures are followed. The sequence of mixing the various ingredients affects the solution stability. Of particular concern is the stability of the fat emulsion, as multiple factors, including pH, glucose, amino acid, and divalent-cation concentrations, can impact the fat emulsion stability (Allwood 2000). Procedural protocols have been developed to help reduce the likelihood of incompatibilities within the formulation (Campbell et al. 2006). First, all trace elements and electrolyte (except phosphorus) should be added to the dextrose solution; second, any phosphorus additives should be mixed with the amino acid solution; third, the amino acid and dextrose

Fig. 21.3. Individual components for manual PN solution compounding.

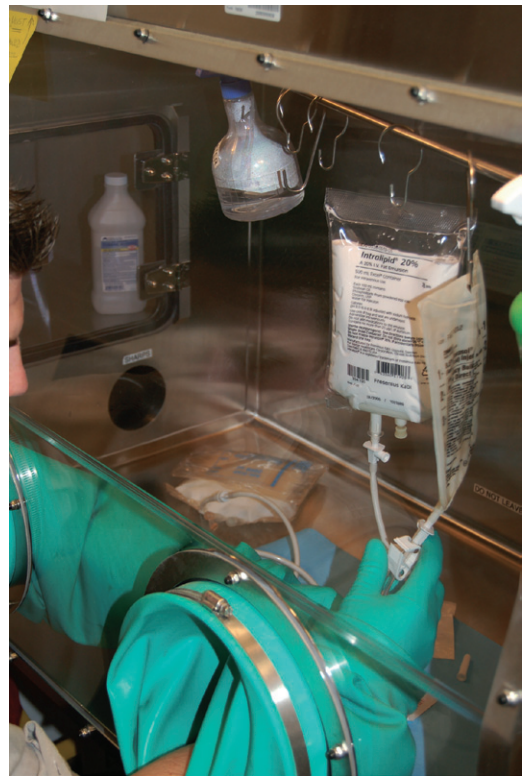

Fig. 21.4. Manual PN solution compounding within a mobile isolation chamber at the University of California, Davis Veterinary Medical Teaching Hospital.

Fig. 21.5. Clean room for automated PN compounding at the University of California, San Diego Medical Center.

Fig. 21.6. An automated compounder used for preparing PN solutions at the University of California, San Diego Medical Center.

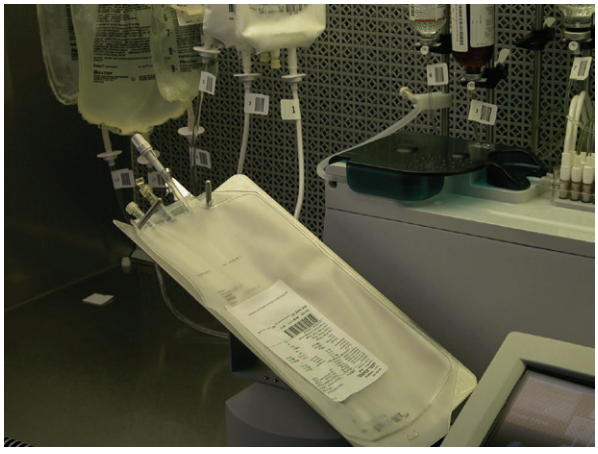

Fig. 21.7. Automated PN solution compounding at the University of California, San Diego Medical Center.

solution should be mixed; fourth, the lipid emulsion should be added to the dextrose and amino acid mixture; and finally, any addition of other medications or components should be considered in accordance with verified stability information (Campbell et al. 2006). Regular visual inspection and monitoring of the quality of the admixture should also be performed, assessing for precipitates and coalescence of fat particles.

While many teaching institutions regularly compound PN solutions, most veterinary practices do not have the appropriate equipment and/or facilities for proper PN

Fig. 21.8. Feline patient at the University of California, Davis Veterinary Medical Teaching Hospital receiving CPN. Note the administration line has been taped to help remind clinic staff not to disconnect the line and to prevent the line from becoming disconnected by the patient.

compounding. Compounding pharmacies that are equipped for human PN preparation will generally compound veterinary formulations. Alternatively, large veterinary referral hospitals or human hospitals in the area may also compound PN solutions and will also commonly work with local veterinarians. Finally, some university veterinary medical teaching institutions provide nutrition support services that provide individual PN formulations, compounding, and delivery.

INITIATING PARENTERAL NUTRITION

PN products should be administered through a dedicated catheter or dedicated port. The administration line should also be dedicated for PN administration only, and should include a 1.2-µm in-line filter to help prevent inadvertent administration of lipid globules or precipitates. To ensure the sterility of the line, it should not be broken during PN administration (i.e., disconnected for patient walks). To help remind clinic staff not to disconnect the line and to prevent the line from becoming disconnected by the patient, it is helpful to tape the line at the connection ports (Fig. 21.8). It is generally recommended to cover the PN bag to prevent degradation of B vitamins by UV light. The PN must be discarded after 24 to 48 hours of hanging, and the administration line should be discarded and replaced with each new bag of PN.

The PN should be administered by continuous-rate infusion over a 24-hour period with the use of a fluid pump. Infusion of daily energy needs over a 10-hour period has

been reported in healthy dogs (Zentek et al. 2003). Successful administration of partial energy needs via PPN over a 10- to 12-hour period has also been reported in hospitalized dogs (Chandler and Payne-James 2006). It has been suggested that higher-fat solutions may be better tolerated than high dextrose-containing solutions for shorter, more rapid rates of infusion (Zentek et al. 2003). Further research in this area is needed and could open up new avenues for more practical uses of PN in veterinary hospitals where 24-hour monitoring is unavailable.

The goal rate of PN administration is determined by the patient's daily energy requirement and the energy density of the solution. The total volume to be administered over the 24-hour period should be equivalent to the patient's calculated RER. The patient should be slowly weaned onto the PN goal rate, starting with 25% of the goal rate, and increasing by 25% increments every 8–24 hours. The rate of weaning onto PN will be dependent on the individual patient response, including the presence of hyperglycemia, hyperlipidemia, and/or electrolyte abnormalities. Guidelines for blood glucose monitoring during the weaning on period are outlined in Table 21.3. Patients who have been without food for an extended period of time are at an increased risk of developing electrolyte abnormalities upon refeeding (see discussion in complications section below). These patients may require a slower rate of weaning on, with more frequent monitoring.

MONITORING GUIDELINES

Careful monitoring is essential during PN administration, especially during the weaning-on period. The guidelines in Table 21.3 give minimum monitoring recommendations. The frequency in which specific parameters should be measured will be driven by the status of the patient. Patients with a poor nutritional status and in a more critical state of illness will require that measurements be taken at an increased frequency. Frequent monitoring is also required if a faster rate of weaning onto PN is desired.

COMPLICATIONS

Complications associated with PN are classified as metabolic, mechanical, and septic. Metabolic complications are the most common, followed by mechanical and then septic. There have been five comprehensive retrospective

Table 21.3. Parenteral Nutrition Monitoring Guidelines*

1. Measure and record body weight, temperature, pulse, and respiration rate daily.
2. Measure blood glucose (BG) every four hours until the goal rate of administration is reached. Start PN administration at 25% of the goal rate (determined by patient's daily RER requirement).
   a. If BG is < 250 mg/dl, increase the rate of administration by 25% of the goal rate until goal rate is reached.
   b. If BG is 250–300 mg/dl, maintain present rate of infusion during the weaning-on period. If infusing at 100% of goal rate and glucose level continues over two measurements at four-hour intervals, consider insulin administration, decrease the rate of infusion by 25%, or decrease the dextrose content of the solution.
   c. If BG > 300 mg/dl, consider insulin administration, decrease the rate of infusion by 25%, or decrease the dextrose content of the solution.
3. Measure packed cell volume (PCV) and total solids (TS), and examine for lipemic serum daily.
4. Measure serum potassium and phosphorus concentrations within 12 hours of starting PN infusion. Continue to measure at a frequency of no less than once daily during the weaning on period, and no less than once every other day once at goal rate of infusion for 24 hours.
5. Measure ionized magnesium within 24 hours of starting PN infusion. Repeat within 48 hours if hypomagnesemia is measured.
6. Measure complete chemistry panel within 24 hours of starting PN infusion, and then no less than once every two to three days.
7. Measure serum triglycerides if lipemic serum is present for two or more consecutive measurements at four-hour intervals.
8. Perform thoracic radiographs if respiratory distress develops any time during administration.
9. Evaluate catheter site twice daily for evidence of infection and/or thrombophlebitis.
10. Perform catheter tip and/or blood cultures if sepsis is suspected.

*Addapted from Delaney, S.J., A.J. Fascetti, and D.A. Elliott. "Critical care nutrition of dogs." 2006. In: *Encyclopedia of Canine Clinical Nutrition*, edited by P. Pibot, V. Biourge, and D. Elliott, 426–447. Italia: Aniwas SAS.

studies reporting complications associated with PN in dogs and/or cats (Lippert, Fulton et al. 1993; Reuter et al. 1998; Chan, Freeman, Labato et al. 2002; Pyle et al. 2004; Crabb et al. 2006). The Lippert study evaluated 72 dogs and 12 cats; the Reuter study evaluated 209 dogs; the Chan study evaluated 80 dogs and 47 cats; the Pyle study evaluated 75 cats; and the Crabb study evaluated 40 cats. The Chan study evaluated patients that received partial energy requirements (delivered both peripherally and centrally) while the other studies evaluated patients that received full energy needs via central venous delivery. Collectively, these studies provide an overview of the common complications associated with PN in dogs and cats.

Metabolic Complications

Hyperglycemia is the most common metabolic complication reported in both dogs and cats. Hyperglycemia was reported in 75% of cats and 31% of dogs in the Lippert study; 32% of dogs in the Reuter study; 12.5% of dogs and 44.7% of cats in the Chan study; 47% of cats in the Pyle study; and 23% of cats in the Crabb study. The Crabb study also reported seven additional cats that were hyperglycemic prior to PN and subsequently developed more severe hyperglycemia. The increased severity of hyperglycemia was not reported; however, by including these seven cats, the total percent of hyperglycemia seen is increased to 40%. This number may be a better comparison, as the Pyle study defined a hyperglycemic complication to include cats with preexisting hyperglycemia with subsequent elevations in glucose of ≥ 100 mg/dL (accounting for 59% percent of the total hyperglycemic cats). The higher incidence of hyperglycemia in the earlier studies may also reflect the shift that has occurred over time from feeding energy levels calculated with high illness energy factors, to more conservative levels of RER only.

Hyperglycemia has been a major topic of interest in both human and veterinary critical care patients in recent years. In the Pyle study, the risk of mortality was increased by greater than fivefold in cats that developed hyperglycemia after the first 24 hours of PN (odds ratio of 5.66). Similar increased risks of mortality have been demonstrated in human patients who develop hyperglycemia during PN administration (Cheung et al. 2005; Lin et al. 2007). Hyperglycemia is not limited to patients receiving PN, and it has been documented in both human and veterinary critically ill patients (Chan, Freeman, Rozanski et al. 2006; Hafidah, Reuter, Chassels et al. 2007). An evaluation of cats that presented to an emergency service at a large referral hospital reported a 40% incidence of hyperglycemia at presentation (Chan, Freeman, Labato et al. 2002). Hyperglycemic cats in this study were significantly more likely to die or be euthanized than those without hyperglycemia. Further evaluation by this same group of researchers revealed that critically ill cats have significantly higher glucose, lactate, cortisol, glucagon, and norepinephrine concentrations, and significantly lower insulin concentrations when compared to controls (Chan, Freeman, Rozanski et al. 2006). These findings are consistent with those from human studies, showing higher concentrations of counter-regulatory hormones and insulin resistance in critically ill patients (Marik and Raghavan 2004; Zauner et al. 2007).

Further research in this area is needed to determine the most appropriate management strategies for hyperglycemic veterinary patients. However, maintaining tighter glycemic control in patients receiving PN may aid to improve patient outcome. Patients who develop hyperglycemia in the initial phases of PN administration should be more slowly weaned onto full administration rates. For those patients who are persistently hyperglycemic, insulin therapy should be implemented, or the parenteral solution should be reformulated to provide a lower carbohydrate concentration.

Hyperlipidemia is also a commonly reported metabolic complication seen in 46% of the dogs and cats in the Lippert study; 7% of the dogs in the Reuter study; 12.5% of the dogs and 19% of the cats in the Chan study; and 15% of the cats in the Crabb study. In contrast, hyperlipidemia was also one of the reported metabolic corrections seen while on PN in the Reuter study. Similarly, in the Pyle study, 24% of cats had hyperlipidemia prior to starting PN, and this value decreased to 19% of cats after 24 hours, and 15% of cats after 96 hours of PN administration. The presence of hyperlipidemia prior to PN administration was not reported in Lippert, Chan, or Crabb studies. The reason for the differences seen between these studies is unclear. However, in the Reuter and Pyle studies, patients with preexisting hyperlipidemia likely reflected those with increased mobilization of fat in response to prolonged anorexia and illness (Wolfe, Shaw, and Durkot 1983). Hyperlipidemia may also have been related complications to poorly regulated diabetes mellitus (Michel 2005). Of the cats in the Pyle study, 17% had diabetes mellitus, but the association between the presence of diabetes mellitus and hyperlipidemia was not evaluated. In addition to the hyperglycemia, elevations in nonesterified fatty acids (NEFA) have also been documented in critially ill cats (Chan, Freeman, Rozanski et al. 2006). In patients such as these, refeeding may help to decreased endogenous break down of fat and actually improve or resolve

hyperlipidemia. Management of hyperlipidemia in patients on PN includes decreasing the rate of administration or reformulation of the parenteral solution to provide a lower fat concentration.

A wide range of electrolyte abnormalities, including hyponatremia, hypokalemia, hypocalcemia, hypophosphatemia, and hypochloremia, were reported in four of the five retrospective studies (Lippert, Fulton et al. 1993; Reuter et al. 1998; Pyle et al. 2004; Crabb et al. 2006). Electrolyte abnormalities are commonly associated with refeeding syndrome. "Refeeding syndrome" is a term commonly used to describe the metabolic abnormalities that can occur upon refeeding a patient following an extended period of anorexia (Crook et al. 2001). These patients often have an intracellular depletion of electrolytes that may not be recognized by evaluation of serum electrolytes. When nutrients are delivered to the patients, either by enteral or parenteral routes, there is an increased need for electrolytes (such as phosphorus and magnesium) to drive metabolic pathways as substrate and cofactors for adenosine triphosphate (ATP) synthesis. This increased intracellular need, in conjunction with cotransport of potassium into the cell with insulin-driven glucose uptake, results in an inward rectification of serum phosphorus, magnesium, and potassium.

As mentioned previously, it is recommended that any additional electrolyte abnormalities be corrected through crystalloid fluid supplementation, as the risk of solution instability or mineral precipitation is greater with additions to PN admixtures. In addition, if reduced concentrations of electrolytes are required after the additions have been made to crystalloid fluids, the cost of replacement is significantly less than replacement of the PN solution.

Hyperbilirubinemia is another common complication reported in patients on PN. Hyperbilirubinemia was seen in 24% of dogs in the Reuter study, and in 4% of the dogs and 6% of the cats in the Chan study. Hyperbilirubinemia was not reported in the Lippert, Pyle, or Crabb studies. Cholestasis and fatty infiltration of hepatic parenchyma has been associated with PN and may have contributed to the hyperbilirubinemia seen in these studies. Although high levels of fat in parenteral solutions can be responsible for this complication, high carbohydrate infusions have also been associated with high activity of hormone sensitive lipase (resulting in endogenous fatty acid release) and can also be a contributing factor (Klein et al. 1998).

Azotemia has also been reported in association with PN, seen in 17% of the dogs and cats in the Lippert study; 5% of the dogs in the Reuter study; 1.3% of the dogs in the Chan study; and 7.5% of the cats in the Crabb study. Azotemia was not a reported complication seen with PN in cats in the Chan and Pyle studies. Azotemia seen with PN administration has been attributed to a combined effect of endogenous (muscle catabolism) and exogenous (PN) amino acids that are rapidly cleared by the liver in critically ill and injured patients (Klein et al. 1998). Animals with preexisting renal disease or who develop azotemia while on PN should be administered or switched to a parenteral solution with a reduced protein level.

Although it has not yet been reported in veterinary patients, respiratory complications associated with hypercapnia secondary to high-caloric and high-carbohydrate administration have been reported in human ventilatory patients (Askanazi et al. 1981; Jannace et al. 1988; Liposky and Nelson 1994; Tappy et al. 1998). Metabolism of carbohydrate generates more carbon dioxide than the metabolism of protein or fat and therefore contributes to the hypercapnia seen in these patients. Carbohydrate levels that resulted in the complications seen in human studies are higher than those generally used in veterinary PN solutions (80% to 100% of nonprotein calories). Although evaluations have not yet been made in dogs and cats, overfeeding and high-carbohydrate solutions should be avoided in patients requiring ventilatory support.

Mechanical Complications

Mechanical complications are the second most frequent type of complication seen with PN. Mechanical complications occurred in 46% of the dogs and cats in the Lippert study, with broken lines being the most common, followed by catheter dysfunction and chewed lines. Mechanical complications occurred in 37% of dogs in the Reuter study, with occluded lines and line disconnections being the most common, followed by leaking lines, chewed lines, jugular vein thrombosis, and perivascular infiltration. In the Chan study, 26% of dogs and 9% of cats had a mechanical complication, with the most common being catheter dislodgement and catheter disconnection, followed by thrombophlebitis, catheter occlusion, and chewed lines. Twenty-one percent of the cats in the Pyle study had at least one mechanical complication, with the most common being dislodgement of the jugular catheter, kinking of the jugular catheter at the suture site, and occlusion of the administration line. In the Crabb study, 28% of the cats had at least one mechanical complication, with catheter dislodgement being the most common, followed by thrombophlebitis/cellulitis and catheter occlusion.

Mechanical complications appear to be more frequent in dogs than in cats, with a higher number of complications that are associated with chewing or breaking the line.

Fig. 21.9. Canine patient at the University of California, Davis Veterinary Medical Teaching Hospital receiving CPN. Note that the administration line is hung and secured to a harness to help prevent mechanical complications.

Some of these complications can be avoided by careful monitoring of the patient, and utilization of restrictive collars and taping of the administration line (Fig. 21.9).

Septic Complications

Although they are generally the least frequent type of complication, septic complications can have severe consequences and are therefore a concern during PN administration. Catheter-related septic complications and contamination of lipid-containing parenteral solutions with microorganisms are two of the primary concerns with PN administration. However, other factors contribute to the septic risks, including the underlying disease of the patient and gastrointestinal bacterial translocation (Harvey et al. 2006).

Despite these many concerns, reports of septic complications with PN administration have been fairly low, especially in recent years. Seven percent of dogs in the Lippert study developed clinical signs of sepsis while on PN that were confirmed with a positive catheter tip or blood culture. Half of these dogs responded within 24 hours to catheter removal, while the other half did not survive. All of the nonsurvivors had severe underlying disease conditions, including severe pancreatitis with concurrent diabetes mellitus and chronic renal disease, septic peritonitis, and severe hemorrhagic enterocolitis. In the Reuter study, 7% of dogs had a septic complications confirmed with a positive catheter tip culture. Three of these dogs (20%) did not survive (underlying disease states were not reported). In the Chan study, 2.5% of dogs and 4% of cats had confirmed sepsis with positive catheter tip cultures. All of these patients where successfully discharged. No septic complications confirmed with positive catheter tip and/or blood cultures where reported in the Pyle or the Crabb studies. In the Pyle study, four cats developed neutrophilia and two cats developed a fever while on PN. In the Crabb study, five cats developed a fever after starting PN. PN could not be specifically implicated in any of these cases reported from the Pyle and Crabb studies.

Contributing factors for the septic complications seen in the above studies included the patient chewing through the administration line, the catheter used for fluid and medication administration prior to use for PN, the catheter placed by an inexperienced operator, poor nutritional status of the patient, and a severe underlying disease state. The decrease in septic complications in more recent studies may reflect implementation of more rigorous monitoring and aseptic techniques, as well as improved experience with PN administration. The Chan study included patients only receiving partial energy requirements and, therefore, may have selected for patients with less severe disease conditions than those in the other studies. Finally, the later studies have evaluated cats only, and all of the reports of sepsis in the Lippert study were in dogs. This may reflect the increased incidence of dogs chewing on administration lines and therefore breaking the aseptic barrier.

Septic complications can be decreased by practicing aseptic techniques during catheter placement and careful maintenance of an aseptic administration line. Use of restrictive collars or 24-hour monitoring may help to ensure that patients do not disrupt the administration line. Appropriate catheter care and replacement protocols, as well as frequent catheter monitoring may help to prevent

and/or identify problems at an early stage (Ukleja and Romano 2007). Finally, early transition to enteral nutrition, or providing a portion of nutritional needs via enteral route, may help to reduce the occurrence of villous atrophy and bacterial contamination (Qin et al. 2002).

DISCONTINUING PARENTERAL NUTRITION

Transition to enteral or oral feeding should be initiated as soon as can be tolerated by the patient (Fig. 21.10). PN has been shown to reduce sham feeding in dogs by 50%, with the mechanism of action likely through peptide YY and neuropeptide Y (NPY) receptor mediated events (Lee, Mannon, Grand, and Pappas 1997). Therefore, when transitioning to oral feeding, decreasing the rate of PN administration may be required to restore the patient's full appetite. Abrupt discontinuation of PN should be avoided, as this can result in hypoglycemia. The rate of PN administration should be slowly weaned, starting with a 25% decrease in administration rate, followed by additional 25% decreases over a 4- to 12-hour time frame with monitoring for hypoglycemia.

Fig. 21.10. Canine patient at the University of California, Davis Veterinary Medical Teaching Hospital being offered oral feedings for transition off of CPN.

SUMMARY

- All hospitalized patients require assessment of nutritional status and consideration as to when assisted feeding should be implemented.
- Parenteral nutrition (PN) is indicated in patients with intractable vomiting and/or diarrhea; anesthesia or lack a gag reflex; recovery from severe gastric or intestinal resection; poor anesthetic candidate for proper feeding tube placement; or inability to meet full energy requirements via enteral route.
- PN may be delivered via central or peripheral venous access.
- Central delivery of PN allows for a greater osmolarity, providing more flexibility in formulations and typically a greater energy density of the solution.
- Caloric distribution of parenteral solutions should be determined on an individual patient basis, taking into consideration individual tolerance of protein, fat, and carbohydrate, and any underlying disease states.
- Metabolic complications are common, requiring frequent monitoring and adjustments.
- Many mechanical and septic complications can be avoided with appropriate monitoring and aseptic techniques.
- Transition to enteral or oral feeding should be initiated as soon as can be tolerated by the patient.

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